Stern, Mike[1]; Hempel, Georg[1]

[1] Institut für Pharmazeutische und Medizinische Chemie, Klinische Pharmazie, WWU Münster, Corrensstraße 48, 48149 Münster, Germany

# Clinical validation study to derive conversion factors from capillary blood to plasma concentration for mirtazapine, quetiapine and norquetiapine

## Introduction

The use of Therapeutic Drug Monitoring (TDM) in the field of psychotropic drugs has increased in the past years. TDM is often recommended to reach the therapeutic reference range faster and to reveal possible non-compliance [1]. In the past years, several new microsampling techniques, which enable a faster and easier TDM, evolved. Some techniques to mention are HemaXis, Dried Blood Spots, the HemaPEN or volumetric absorptive microsampling (VAMS) with the so-called Mitra®-devices. Since therapeutic reference ranges are defined in plasma concentrations, conversion factors from capillary blood to plasma concentrations have to be derived with clinical validation studies.

## Methods

A clinical validation study was conducted with two hospitals in Münster, Germany. Patients gave written informed consent and three Mitra® samples were drawn for each patient. While a venous blood sample was routinely drawn, an additional capillary blood sample was taken at the same time. The venous blood was then sampled with a Mitra®, centrifuged and the plasma supernatant was also sampled with a Mitra®. All three samples were sent to a laboratory and quantified with a single-quadrupole HPLC-MS. The results were plotted with Passing-Bablok regression and the derived conversion factors were validated with Bland-Altman-analysis.

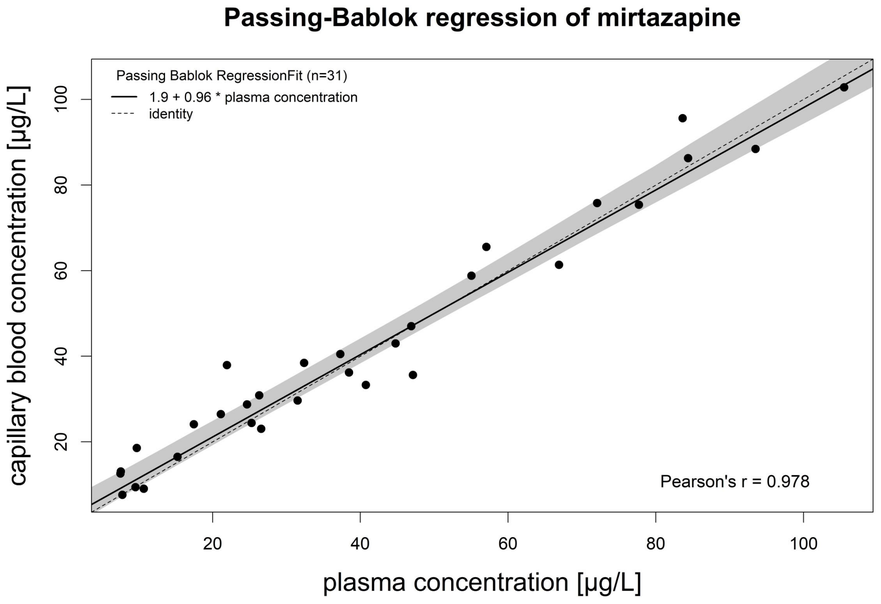
## Results

Table 1: Slopes, Pearson's R, intercept and confidence intervals for the comparison of capillary blood, venous blood and plasma concentration for mirtazapine, quetiapine and norquetiapine. Table at bottom excluded one patient with three samples in the study.

| Substance | n | Comparison | R | Slope | LCI | UCI | Intercept | LCI | UCI |
|---|---|---|---|---|---|---|---|---|---|
| Mirtazapine | 31 | capillary to plasma | 0.978 | 0.96 | 0.90 | 1.06 | 1.90 | -0.64 | 6.21 |
| | 31 | venous to plasma | 0.967 | 0.95 | 0.87 | 1.06 | 2.01 | -1.27 | 4.57 |
| | 31 | capillary to venous | 0.981 | 1.00 | 0.93 | 1.08 | 0.59 | -2.31 | 3.97 |
| Quetiapine | 16 | capillary to plasma | 0.957 | 0.74 | 0.62 | 1.23 | 0.07 | -12.32 | 7.62 |
| | 16 | venous to plasma | 0.966 | 0.71 | 0.60 | 0.93 | 1.74 | -4.36 | 8.30 |
| | 16 | capillary to venous | 0.997 | 1.12 | 1.01 | 1.20 | -3.50 | -6.74 | -0.41 |
| Norquetiapine | 16 | capillary to plasma | 0.863 | 0.90 | 0.64 | 1.62 | -0.28 | -4.79 | 5.27 |
| | 16 | venous to plasma | 0.874 | 0.92 | 0.67 | 1.47 | -0.60 | -5.84 | 7.56 |
| | 16 | capillary to venous | 0.995 | 0.99 | 0.92 | 1.05 | -0.07 | -1.02 | 0.95 |

| Substance | n | Comparison | R | Slope | LCI | UCI | Intercept | LCI | UCI |
|---|---|---|---|---|---|---|---|---|---|
| Mirtazapine | 28 | capillary to plasma | 0.982 | 0.97 | 0.90 | 1.09 | 0.86 | -2.14 | 6.40 |
| Quetiapine | 13 | capillary to plasma | 0.955 | 0.67 | 0.62 | 1.18 | 0.94 | -11.87 | 4.34 |
| Norquetiapine | 13 | capillary to plasma | 0.892 | 0.87 | 0.63 | 1.35 | -0.22 | -4.75 | 4.94 |

Legend: n: sample size; R: Pearson's R; LCI: lower confidence interval; UCI: upper confidence interval



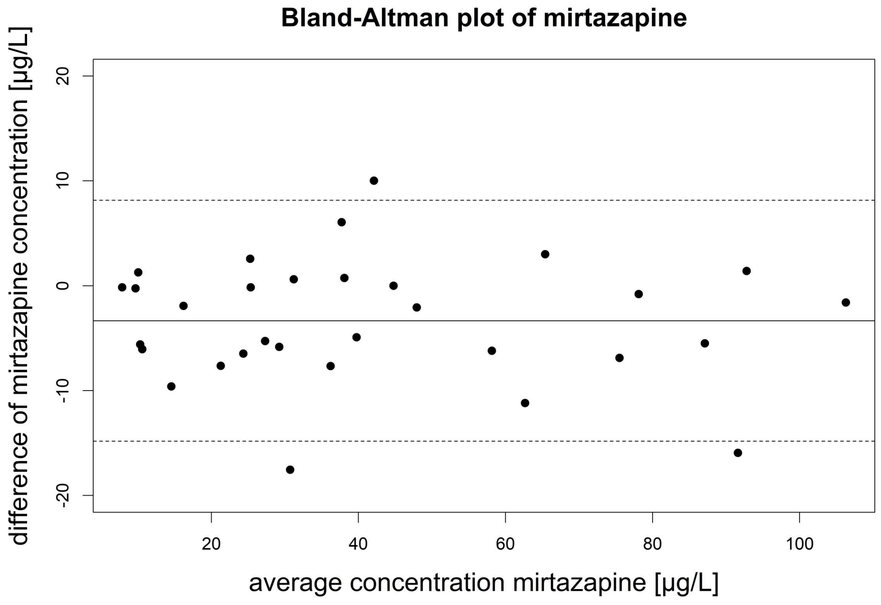




Figure 1&2: Passing-Pablok regression and Bland-Altman plot for mirtazapine

## Conclusions

The clinical validation study showed a good regression between capillary blood concentration and plasma concentration for mirtazapine and quetiapine. The sample size for norquetiaopine was too small so the Bland-Altman analysis was not passed for this substance. The conversion factors 1.03 for mirtazapine and 1.49 for quetiapine can be used for TDM with capillary blood sampling.

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## References

[1] C. Hiemke et al, *Pharmacopsychiatry*. **2018, 51, 9-62.**

## Contact

Corrensstraße 48
48149 Münster
Raum: A120.209

Tel.: 0251/83-32171
mail: m.stern@uni-muenster.de