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Quantification of Pharmacokinetic Interactions: MDDI-Calculator of the Scholz-Datenbank vs. Physiologically-Based Pharmacokinetic Modeling (PBPK)

Introduction
Nowadays, polypharmacy plays an immense role in both clinical and ambulatory care. Patients are treated with drugs, which are influencing each other, so their plasma concentrations may increase or decrease. Especially the inhibition of liver enzymes like cytochrome P450 oxidases (CYP) provokes a higher risk for side effects. So, there is a great relevance to predict the possible extent of a pharmacokinetic interaction e.g. if a dose reduction is useful when those drugs are combined.

Methods
With their agreement, fourteen (5 male, 9 female) inpatients at Alexander Hospital in Münster [Table 1], who are treated with the combination of both the antidepressants mirtazapine and venlafaxine, were recruited. In the context of therapeutic drug monitoring, samples were taken via Dried-blood-spot method.

Afterwards, the plasma concentrations of mirtazapine were determined by LC-MS. The MDDI Calculator of the Scholz-Datenbank allows the prediction to what extent an inhibitory drug influences the area under the curve (AUC/exposition) of another drug. Venlafaxine’s potential weak inhibitory effect on CYP 2D6 and the extent of mirtazapine’s metabolism is processed through the same enzyme are illustrated in Table 2 as well as relative changes of AUC and dose are displayed.

Results
The created models of dose-corrected immediate release (IR) mirtazapine [Figure 1] and of 75 mg extended release (ER) venlafaxine [Figure 2] show in the goodness-of-fit (GOF) plot a good predictive capability.

Conclusions
The PBPK model does not show any impact on the metabolism of mirtazapine by venlafaxine in contrast to the MDDI Calculator of SCHOLZ Databank. To evaluate the model’s clinical relevance more clinical research and comparison is needed including other CYP2D6 substrates, inhibitors and pharmacogenomics.

Literature/References
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