Improving Precision Medicine by reconciling drug interaction checking with pharmacogenetics and renal status of the patient

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Introduction
The general theory of “multi drug drug interactions (MDDI)“ has been developed to support the assessment of relative changes of AUC (AUCrel) and dose (Drel) of a drug based on the interplay of all substrate properties and drug interaction mechanisms for all drugs involved as inhibitors (1). Drug drug interactions (DDI) may mimic the impact of polymorphism at transporters and enzymes (2). That applies also to variant stages of renal failure caused by CKD. The mathematics of changes in total drug clearance due to renal failure are much better known than those due to hepatic failure. Therefore polymorphism and renal failure as expressed by the individual patient should be well included into the model of computing changes of drug absorption or elimination as implemented in the MDDI Calculator of drug interaction software such as DIT Drug Database* (USA) and SCHOLZ Database** (Germany).

Polymorphism
Literature about polymorphism and DDI reveals that practically those effects play the major role where CYP2D6, CYP2C19 and CYP2C9 are involved in drug metabolism; furthermore, when looking at the consequences from polymorphism precise recommendations especially for dosing have been published for the genetic EM or PM status and to much lesser extent for UM or IM status (2, 3, 4, 5). The focus of integration and validation of polymorphisms in the MDDI system lies therefore on the phenomena which show how assessments of AUCrel (AUC) or Drel (D) of MDDI Calculator (MDDI) compare with in-vivo study data or recommendations (Study/Rec) focussing on clinical information for CYPs mentioned above and genetic status EM or PM (Status) as displayed in Table1.

Aripiprazole kinetics (see Screenshot 1 on Poster “1”) for an EM treated with only a CYP3A4 blocker on top; this accords to the idea of the mimic effect of DDI mentioned above and to clinical findings and recommendations (4, 5).

Screenshots 1-3 illustrate for a complex scenario with aripiprazole which is also shown in Table 2 the interplay of DDI, polymorphism, and renal failure (from german SCHOLZ Database software: CKD 4 = NI 4).

Table 1: Drugs Status MDDI Study/Rec Lit
Paroxetine 2D6 PM 0.49 (D) 0.5 (D) 4
Fluoxetine 2D6 PM 0.04 (D) 0.05 (D) 5
Eli Lilly 2C19 PM 0.5 (D) 0.5 (D) 4
Sertraline 2C19 PM 0.5 (D) 0.5 (D) 4
Haloperidol 0.5 (D) 0.5 (D) 2
Zuclopenthixol 0.5 (D) 0.5 (D) 2
Metoprolol 2D6 PM 0.28 (D) 0.25-0.30 (D) 2
Metoprolol 2D6 PM 0.38 (AUC) 0.35 (AUC) 14,16,17,18
Propafenon 2D6 PM 0.62 (D) 0.25-0.30 (D) 2
Propafenone DDI 1.90 (AUC) 1.5 (AUC) 8
Flecaïnide 2D6 PM 0.37 (D) 0.3 (D) 2
Aripiprazole-Fluoxetine-Chlorthiamycin 2D6 EM 0.25 (D) 0.25 (D) 5
Aripiprazole-Chlorthiamycin 2D6 PM 0.25 (D) 0.25 (D) 5

Table 2: Drugs Stage* MDDI Study/Rec Lit
Meflozin a) CKD 3 0.45 (D) 0.45 (D) 14, 15
Fosfomycin a) CKD 4 0.24 (D) 0.24 (D) 13
Aripiprazole CKD 4 0.79 (D) 0.79 (D) 14, 16
Aripiprazole-Fluoxetine-CKD 4 0.53 (D) 16, 17,18
Aripiprazole-Fluoxetine-CKD 4 0.32 (D) 16, 17,18
Aripiprazole-Fluoxetine-CKD 4 0.32 (D) 16, 17,18
Aripiprazole-Fluoxetine-CKD 4 0.32 (D) 16, 17,18
Rivaroxaban CKD 4 1.49 (AUIC) 1.6 (AUIC) 19
Rivaroxaban-Chlorthiamycin CKD 4 1.33 (AUIC) 1.5 (AUIC) 19
Rivaroxaban-Chlorthiamycin CKD 4 2.95 (AUIC) 19
Rivaroxaban-Ketoconazol CKD 4 2.58 (AUIC) 2.6 (AUIC) 19
Rivaroxaban-Erythromycin CKD 3 1.29 (AUIC) 1.3 (AUIC) 19
Rivaroxaban-Erythromycin CKD 3 1.84 (AUIC) 2.0 (AUIC) 19

Table 3: Observations and Conclusions
1. Establishing one theory and model to handle DDI, polymorphism and renal failure all in one seems feasible. Therefore, achieving more precision medicine in solving complex problems in the treatment of multimorbide patients in the general practice is close to come true.
2. Consistency of MDDI Calculator assessments and clinical data has been confirmed for drug scenarios with polymorphism, renal failure, and DDI solely and in complex interplay. Prediction accuracy can be judged practically those discrepancies are in general less than 24% (9).
3. Clinical information for DDI and polymorphism may deviate sometimes clearly from each other due to calibrating the MDDI Calculator mainly based on DDI (e.g., Propafenone, Haloperidol); further exploration is needed in these cases.

         * DIT Drug Database is product of DIT mondial, USA. ** SCHOLZ Datenbank is product of ePrax GmbH, Germany. These products are protected by nat. and internat. copyright laws

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Screening 1: Impacts on Bioavailability

Screening 2: Impacts on Metabolism and Elimination

Screening 3: Assessments for AUCrel and Drel

References
1. Improving Precision Medicine by reconciling drug interaction checking with pharmacogenetics and renal status of the patient

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