The MDDI Calculator: Moving drug interaction checking in polypharmacy away from the traditional model towards Precision Medicine

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Introduction
The traditional way of checking drug drug interactions (DDI) is based on analysing pairs of drugs. In polypharmaceutical scenarios this model may produce lots of alerts. As drugs may be subject to multiple interactions by multiple drugs the user has to puzzle together tediously what is really the compiled essence and conclusion for drug therapy. Therefore, this kind of analysis is far away from practicing precision medicine.

Modelling and validating a theory to handle multiple Drug Drug Interactions (MDDI)
What is the impact on one drug by all other drugs in the medication? To answer this question a more 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 changes of bioavailability F and elimination constant Kel through the interplay of all substrate properties and drug interaction mechanisms for all drugs involved as inhibitors (1):

\[ \text{AUCrel} = \frac{F_{rel}}{K_{rel}} \]
\[ \text{Drel} = \frac{K_{rel}}{F_{rel}} \]

The DDI software of DIT Drug Database* (USA) and SCHOLZ Databank** (Germany) has been supplemented by the MDDI Calculator and validated for some 300 oral drugs.

Table 1 contains examples from the validation process which show how AUCrel assessments of MDDI Calculator (AUCcomp) compare with in-vivo study data (AUCstudy). Screenshot 1 illustrates how substrate aripiprazole is affected by concomitant treatment with both CYP2D6 inhibitor paroxetine and CYP3A4 inhibitor clarithromycin.

* 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

### Table 1:

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUCstudy</th>
<th>AUCcomp</th>
<th>Lit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>0.251</td>
<td>0.25#</td>
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</tr>
<tr>
<td>Loperamide-Geftizobin</td>
<td>2.06</td>
<td>3</td>
<td></td>
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<tr>
<td>Loperamide-Fluconazole</td>
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<td>3.6</td>
<td>3</td>
</tr>
<tr>
<td>Loperamide-Geftizobin-Fluconazole</td>
<td>12.6</td>
<td>12.9</td>
<td>3</td>
</tr>
<tr>
<td>Midaconazole (v.i.)</td>
<td>3.4</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Midaconazole (oral)</td>
<td>8.96</td>
<td>8.44</td>
<td>4</td>
</tr>
<tr>
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<td>1.4</td>
<td>5</td>
</tr>
<tr>
<td>Repaglinide-Geftizobin</td>
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<td>7.6</td>
<td>5</td>
</tr>
<tr>
<td>Repaglinide-Geftizobin-Fluconazole</td>
<td>18.3</td>
<td>18.9</td>
<td>5</td>
</tr>
<tr>
<td>Simvastatin-Clarithromycin</td>
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<td>10.13</td>
<td>6</td>
</tr>
<tr>
<td>Simvastatin-Fluconazole</td>
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<td>17.28</td>
<td>7</td>
</tr>
<tr>
<td>Warfarin-Fluconazole</td>
<td>2.18</td>
<td>1.95</td>
<td>8</td>
</tr>
</tbody>
</table>

* First recommended; # Drel computed, & relative INW

Screenshot 1 illustrates also how pharmacokinetic interactions may be reconciled with side effects and toxicity of all drugs involved, including cumulation of dynamic effects. The therapeutic index of drugs kinetically affected is classified in the MDDI protocol, that helps additionally to assess the relevance of the clinical effects caused by the kinetic interaction, see also explanatory text in Screenshot 1.

Observations and Conclusions
1. Strong enzyme inhibitors may differ in their potency to affect other drugs substantially contradictory to published and official "rough" classifications (9, 10); see simvastatin interactions, Table 1!;
2. Inhibitors may show very different impacts on oral and i.v. drugs demonstrating that blocking e.g. CYP3A4 may cause a bigger contribution to AUC-changes than blocking hepatic CYP3A4; see midazolam interactions in Table 1!
3. Multiple smaller interactions may reach or surpass in their compiled magnitude the effects of interactions between a highly sensitive substrate and a strong inhibitor; compare simvastatin and other multiple interactions in Table 1! (11)
4. Clinical reports about enhanced drug effects or multiple drug interactions can be well explained using the MDDI Calculator (8, 12) as well as recommended dosing of aripiprazol in polypharmacy (2, see also Table 1);
5. Reconciling kinetic and dynamic adverse and cumulative effects creates more transparency for clinical judgements.
6. The validation of the MDDI Calculator has shown that 83% of the assessments deviate less than 10%, 95% less than 20%, and 98% less than 30% from the clinical measurements. Prediction accuracy of the MDDI Calculator is therefore very high as discrepancies less than 24% are judged as "excellent" in the literature (11).
7. Clinical data about multiple drug drug interactions is rare, more clinical research is needed and has been initiated.
8. Billions of different polypharmacy medications with more than 5 or 6 drugs may be prescribed by doctors. It can be assumed that 10% of the population in the industrialized countries, in particular older people, are multimorbid and are prescribed 5 and more drugs permanently (13). Clinical exploration of all these complex combinations and their adverse outcomes is not financeable.
9. Therefore, tools like the MDDI Calculator are necessary to predict and assess risks from multiple kinetic DDI in their often unexpected magnitude and to improve and accelerate decision making in polypharmacy scenarios in the sense of precision medicine.

### Literature:
is available on request

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