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Predicting Changes of Drug Exposure in Pharmacokinetic Pairwise and Multiple Drug Drug Interactions (MDDI)

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Abstract

51 drug drug interactions were evaluated by comparing drug exposure values (AUC) assessed based on pharmacokineticly relevant drug properties with published in vivo data. For this purpose the MDDI Calculator of SCHOLZ DataBank was used. It can be concluded that the MDDI Calculator is able to compute changes of drug exposure in pairwise kinetic DDIs in a very reliable and excellent manner. Furthermore, based on the property settings of ingredients according to the available pairwise in vivo data, AUC changes for multiple pharmacokinetic drug drug interactions (MDDI) may be predicted. The predictive power of the MDDI calculator for multiple drug drug interactions is very well confirmed when looking at the few multiple drug drug interactions where in vivo data is available. Regarding in summary all 51 pairwise and 3 triple drug drug interactions researched, the AUC values, in all cases assessed with less than +- 10% deviation from in vivo data, surpassed substantially the set "excellency" target range of 100% +- 24%.

Introduction

A theory of Multi(Ple) Drug Drug Interactions (MDDI) and its impact on the assessment of pharmacokinetics and adverse effects of drugs has been published in 2016 [1]. The MDDI Calculator of SCHOLZ Databank was the result of the translation of this theory into a drug search engine software with the target to compute and predict changes of drug exposure and dose adjustments in complex drug interaction scenarios in a reliable and fast manner whereby the formulas should preferably relate to basic pharmacokinetic equations and be confined to simple basic mathematical rulings.

The vision to realize such a search engine required to abandon the traditional model of Drug Drug Interactions (DDI) analyzing solely pairs of drugs and to develop a more general theory of Multi Drug Drug Interactions (MDDI). In this theory the relevant pharmacokinetic parameters of drug exposure such as AUC and dose and their relative changes are derived and assessments computed according to kinetic rulings based on the interplay of all properties and drug interaction mechanisms for all drugs involved as substrates or inhibitors of transporter and enzyme systems in absorption, metabolism and elimination.

The fundamental pharmacokinetic relationship for AUC as function of bioavailability F and elimination constant K_{el} is **[2]**:

$$AUC \sim F/K_{el}$$

This applies also for relative changes due to drug drug interactions:

$$AUC_{rel} \sim F_{rel}/K_{elrel}$$

F and K_{el} are furthermore functions of the properties of the substrates and the inhibitors/inducers, which affect transport, metabolism, and elimination. These properties are converted into the relevant kinetic values in a more refined and aggregated manner using % scales compared to the rougher classification of the FDA **[3]**, which assigns inhibitors to three classes:

- weak inhibitors: increase the AUC of a sensitive substrate by factor 1,25 – <2
- moderate inhibitors: increase the AUC of a sensitive substrate by factor 2 – 5
- strong inhibitors: increase the AUC of a sensitive substrate by more than factor 5.

Simple considerations lead to the conclusion that refinement of the FDA system is necessary: A “moderate” inhibitor may increase the plasma level of a substrate by factor 2 or 4,99. In the first case, a dose reduction to half of the original dose may be necessary, in the second case the dose should be reduced to a fifth of the original dose. These differences of the AUC changes are obviously high and particularly in cases of narrow therapeutic index not acceptable. Thus, the sole use of the three FDA classifications may be helpful to classify drug properties roughly, but it is not precise enough to assess the correct dose adjustments due to kinetic interactions.

The MDDI Calculator of SCHOLZ Databank regards each transporter or metabolizing enzyme as a biochemical micro engine the performance of which depends on the propensity of a substrate to be transported or metabolized (STPR/SMPR = Substrate Transporter/Metabolizing Pathway Relevance in %) and the propensity of an inhibitor to block the process and controlling thereby the TransPorter/Metabolizing Enzyme Capacity (TPC/MEC in %) affecting F/F_{rel} as function of F (absolute bioavailability), FP (First Pass Effect), TPC and K_{el}/K_{elrel} (elimination constant in %/h) as function of SMPR and MEC. Applying different propensity settings for all micro engines involved and aggregating such settings in a multidimensional model $AUC_{rel} = AUC_{comp}$ values of a substrate can be electronically computed and tapered to consistency with in vivo study $AUC_{rel} = AUC_{study}$ values whereby AUC_{rel} is defined as the quotient of the AUC affected by an inhibitor and the AUC under normal conditions

$$AUC_{rel} = [AUC_{inh}]/[AUC]$$

Early attempts in the development to calibrate the MDDI Calculator showed good consistency of computed AUC values and in vivo measurements published in the literature **[1]**. Literature presenting in vivo data about multiple drug drug interactions such as published by Niemi et al. **[4,5]** with at least two inhibitors affecting the kinetics of a

substrate is rare. The confirmation of the MDDI method for multiple interactions could therefore only be performed based on these studies by Niemi et al. for repaglinide and loperamide as substrates, and additionally for aripiprazole in consistency with PBPK simulation data **[6]**.

Table 1 compares the in vivo results of Niemi et al **[4,5]** for inhibitor scenarios with the triple drug drug interactions of loperamide – itraconazole – gemfibrozil and repaglinide – itraconazole – gemfibrozil and the consecutive assessment of the AUC_{rel} values with the calculations of the MDDI Calculator of SCHOLZ DataBank.

Table 1: AUC data from in vivo investigations compared with values from the MDDI calculator of Scholz Databank.

Drugs	relative AUC (in vivo data) [4,5]	relative AUC calculated with the MDDI Calculator of Scholz Databank
Repaglinide–Itraconazole	1.4	1.4
Repaglinide–Gemfibrozil	8.1	7.6
Repaglinide–Itraconazole–gemfibrozil	19.4	18.9
Loperamide–Itraconazole	3.8	3.6
Loperamide–Gemfibrozil	2.2	2.1
Loperamide–Itraconazole–gemfibrozil	12.6	12.9

Complex MDDI scenarios consist frequently of multiple pairwise DDIs; therefore it is necessary that the search engine processes traditional kinetic DDIs and computes assessments of drug exposure changes in a reliable way. Consequently drug interaction studies, which represent AUC changes of pairwise interactions were used to calibrate the MDDI Calculator and refine drug properties for precise calculations, if needed.

This contribution shall elucidate the process of calibration of the computational results of the MDDI Calculator. It focuses for that purpose on the interplay of clinically important CYP2D6 substrates **(Table 2)** and inhibitors as these substrates and their metabolism depend in most cases decisively on this enzyme. The fact that some of these substrates depend also on other enzymes such as CYP3A4 yields the advantage, however, that beyond the basic comparison of pairs of drugs the MDDI aspect of multiple drug drug or enzyme interactions can be included. Literature referred to include in vivo data from drug drug interaction studies as well as studies dealing with polymorphism as the patient conditions of Poor Metabolizer (PM) or Intermediate Metabolizer (IM) deteriorating the metabolism of a drug accord usually very well to the impacts of strong or moderate enzyme inhibitors **[7]**.

Predicting AUC values compared to observed values is classified in the literature as “excellent” if deviations in the range of 8 – 24% are achieved **[8]**. Both, the European Medicines Agency (EMA) and the U.S Food and Drug Administration consider that bioequivalence is demonstrated, if the 90% confidence interval for the ratio of the generic and the original drug is between 80% and 125% **[9,10].**

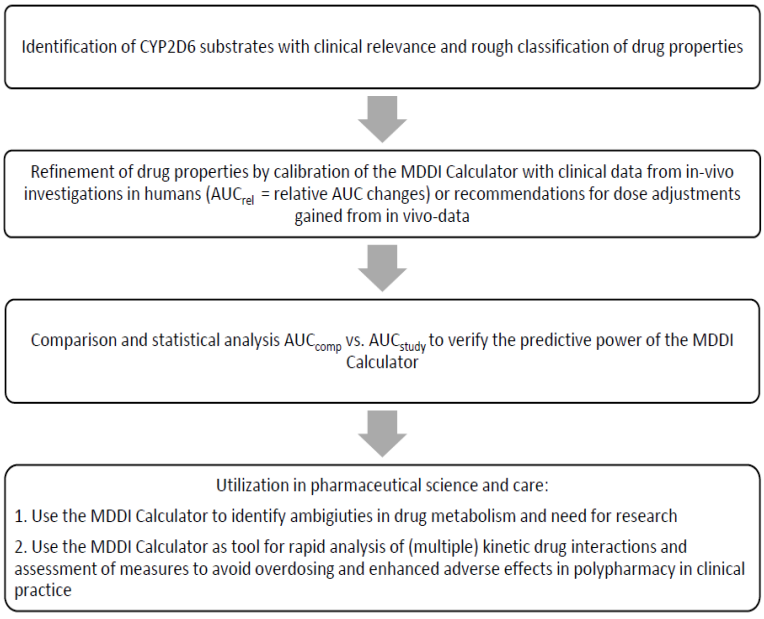
The target of this study was to achieve maximum deviations of ≤ 24% whereas in the best case AUC_{comp} = AUC_{study} equals 100%. Accordingly, the target shall be achieved when the confidence interval for the assessed AUC_{rel} = AUC_{comp} values falls into the interval of AUC_{rel} = AUC_{study} = 100% ± 24%.

Furthermore, the propensities of metabolism or inhibition of ingredients mentioned above shall be ideally unique for the ingredients involved with the consequence that for example the SMPR setting for metoprolol controlling the metabolism at CYP 2D6 is always the same no matter which inhibitor such as fluoxetine, paroxetine, mirabegron or others with different strengths are interacting. Therefore, consistency of assessments made for substrates for which in vivo data with different inhibitors is available shall be researched.

Most cytochrome P450 (P450 or CYP) enzyme catalyzed reactions are adequately described by classical Michaelis-Menten kinetic parameters (e.g., K_m and V_{max}) **[11]**. As drug therapy implies normally very low drug plasma levels the elimination adheres usually to first order or linear kinetics and the total elimination constant K_{el} can be computed as the sum of all process constants K_{el1}, K_{el2}… K_{eln} and their relative values, respectively, involved in metabolism and elimination **[2,12]**. All assessments in this contribution are therefore made under the assumption of such Michaelis-Menten kinetic conditions, too.

Methods

Workflow



Identification of drugs which are metabolized by CYP2D6 and data extraction for basic settings

The identification and classification of drugs, which are metabolized by CYP2D6 and may be inhibited in a clinically relevant manner, was conducted with the help of the classic DDI system of the U.S. SCHOLZ DataBank **[13],** predominantly used for E-prescribing, which is based on the evaluation of literature and professional product information for more than 40 years; especially supportive was also literature concerning dose adjustments in patients with CYP2D6 poor metabolizer status mimicking DDIs with strong inhibitors as presented in the comprehensive

pharmacogenetic study of Kirchheiner et al. **[14].** The suitable drugs for which relative AUC values (AUC_{study}) from in vivo studies in human subjects were available are listed in **Table 2,** in case including hints to additional enzymes impacting the kinetics. Prodrugs such as codeine, tramadole, tamoxifen or drugs where the inhibition of the CYP2D6 metabolism does not change the drug's active moiety and has no impact on the clinical effect and the dosing such as venlafaxine **[28,40]** were excluded.

Table 2: Listing of CYP2D6 substrates including Comparison of calculated AUC values (AUC_{comp}) and literature data (AUC_{study}) after adjustment of drug properties with deviation factors.

Substrate	Inhibitor	AUC_{comp}	AUC_{study}	Deviation Factor	Literature
Amitriptyline	Ketoconazole[2]	126%	135%	93%	**17**
Amitriptyline	PM/Paroxetine[6]	166%	156%[6]	106%	**14**
Aripiprazole	Ketoconazole[2]	152%	163%	93%	**6,7**
Aripiprazole	Itraconazole[2]	148%	148%	100%	**18**
Aripiprazole	Paroxetine[1]	202%	207%	98%	**6,7**
Atomoxetine	Paroxetine	561%	579%	97%	**19**
Clozapine	Fluvoxamine[234]	302%	300%	101%	**20**
Desipramin	Fluoxetin[5]	416%	400%[5]	104%	**21,22**
Desipramine	Mirabegron	324%	341%	95%	**51**
Desipramine	Paroxetine[5]	404%	411%[5]	98%	**21,22**
Desipramine	Sertraline	139%	134%[5]	104%	**43,44**
Duloxetine	Fluvoxamine[4]	602%	600%	100%	**23**
Galantamine	Ketoconazole[2]	128%	130%	98%	**24**
Galantamine	Paroxetine	142%	140%	101%	**24,25**
Haloperidol	Itraconazol[2]	156%	155%	101%	**26**
Haloperidol	Paroxetine[7]	153%	154%	99%	**27**
Haloperidol	Venlafaxine	170%	170%	100%	**28**
Imipramine	Paroxetine[5]	372%	407%[5]	91%	**14,22**
Imipramine	Fluoxetine[35]	386%	407%[5]	95%	**14,22**
Imipramine	Fluvoxamine[34]	359%	363%	99%	**22**
Mirtazapine	Fluoxetine	132%	132%	100%	**29**
Mirtazapine	Paroxetine	117%	117%	100%	**29**
Metoclopramide	Fluoxetine	177%	189%	94%	**30**
Metoprolol	Dronedarone	162%	160%	101%	**47**
Metoprolol	Eliglustat	214%	210%	102%	**48**
Metoprolol	Escitalopram	211%	200%	106%	**49**
Metoprolol	Imatinib	124%	123%	101%	**50**

Metoprolol	Mirabegron	315%	329%	96%	**51**
Metoprolol	Paroxetine[5]	388%	407%[5]	95%	**52-54**
Metoprolol	Propafenone	367%	350%	105%	**55**
Metoprolol	Ranolazine	177%	180%	98%	**56**
Metoprolol	Venlafaxine	137%	140%	98%	**57**
Mianserin	PM/Paroxetine[6]	153%	154%[6]	99%	**14**
Nortriptyline	PM/Paroxetine[6]	266%	251%[6]	106%	**14**
Paroxetine	PM/Fluoxetin[6]	177%	173%[6]	102%	**14**
Perphenazine	PM/Paroxetine[6]	404%	416%[6]	97%	**14**
Pirfenidon	Fluvoxamine[34]	404%	400%	101%	**58**
Propafenone	Fluoxetine	160%	150%	107%	**55**
Propranolol	Dronedaron	130%	130%	100%	**47**
Risperidone	Erythromycin	120%	110%	109%	**59**
Risperidone	Fluoxetine	135%	140%	96%	**59**
Risperidone	Paroxetine	135%	130%[5]	104%	**59**
Tamsulosin	Ketoconazole[2]	263%	280%	94%	**60**
Tamsulosin	Mirabegron[5]	147%	154%[5]	95%	**51,61**
Tamsulosin	Paroxetine	153%	164%	93%	**60**
Thioridazine	Fluvoxamine[4]	303%	300%	101%	**62**
Thioridazine	PM/Paroxetine[6]	297%	313%[6]	95%	**14**
Trimipramine	PM/Paroxetine[6]	374%	365%[6]	102%	**14**
Vortioxetine	Bupropion	240%	228%	105%	**35**
Vortioxetine	Ketoconazole[2]	126%	130%	97%	**35**
Vortioxetine	Fluconazole[2,3]	142%	146%	97%	**35**

[1]AUC study for quinidine as strong CYP2D6 inhibitor

[2]AUC study with CYP3A4 related inhibition

[3]AUC study with CYP2C19/C9 related inhibition

[4]AUC study with CYP1A2 related inhibition

[5]average value from more than one publication

[6]AUC_{study} calculated from recommendations of dose adjustments for poor metabolizers (AUC_{rel} = $(1/D_{rel})*100$), which result from several studies [14]

[7]AUC_{study} from measurements in subjects with poor metabolizer status

Basic settings and refinement of drug properties for AUC_{rel} assessments

SCHOLZ DataBank assigns default % values for the relevant kinetic parameters to drugs which are according to literature in a minor, moderate or major way either substrates dependent on an enzyme/transporter or inhibitors of such enzyme/transporter as listed in **Table 3.**

Table 3: Default SMPR and MEC values are assigned according to the following table.

Pharmacokinetic property	class	% value	comment
SMPR	Major substrate	80%	Assumption: SMPR always < 100%
SMPR	Moderate substrate	40%	
SMPR	Minor substrate	20%	
MEC#	Major inhibitor	1%	Assumption: remaining MEC >= 1%, also with strongest blocker, e.g. paroxetine at CYP2D6
MEC#	Moderate inhibitor	28%	
MEC#	Minor inhibitor	56%	
# Assumptions made for MEC apply also to TPC			

The minimum value for MEC is set to 1% when strongest enzyme blocker such as paroxetine at CYP2D6 or ketoconazole at CYP3A4 are involved; that is in accordance with literature asserting that even at high concentrations inhibition does not approach zero **[11]** and helps also to avoid in case unresolvable fractions.

By adjusting pharmacokinetic properties and repeated comparisons AUC_{rel} = AUCcomp may be electronically tapered to consistency with AUC_{rel} = AUC_{study} whereby the propensity settings of substrates and inhibitors should ideally remain stable in all computation scenarios compared. In exceptional cases where the AUC_{comp} value could not be reconciled by refinement of SMPR or MEC values with the AUC_{study} value in a satisfactory manner placeholder enzymes were in case introduced (see discussion).

Deviations of AUC_{rel} = AUCcomp values from AUC_{rel} =AUC_{study} values are computed by computing the quotient AUC_{comp}/ AUC_{study} as Deviation Factor in %.

Statistical methods

To compare the computed data AUC_{comp} and the in vivo data AUC_{study} the Deviation Factor for each interaction was calculated as follows

$$Deviation\ factor = \frac{AUC(comp)}{AUC(study)} * 100\ \%$$

Even though more than thirty data sets are available, the Shapiro Test for normality was performed to confirm the explored data (AUC_{comp},) show standard Gaussian distribution. Consequently a statistical analysis was made using a two sided one sample Student t-Test for all AUC_{comp}/AUC_{study} values applying an error probability of $\alpha = 0.05$. Not to reject H0 (“no significant differences between study and computed data”) demands that the 95% confidence interval of the Deviation Factor must be within 100% +-24%. Triple combinations were not included in the overall statistics.

Results

Traditional pairwise drug drug interactions (DDI)

Comparisons of in vivo measured relative values for AUC changes with assessments of the MDDI Calculator were conducted for 51 pairwise drug combinations. 44 comparisons related to CYP2D6 substrates affected by CYP2D6 inhibitors or poor metabolizer Status. These comparisons are contained in **Table 2.**

Comparisons for 7 of the substrates investigated related to enzyme CYP3A4 which may be affected additionally.

Multiple drug drug interactions (MDDI)

Comparisons of 5 substrates relate to multiple drug drug, respectively enzyme interactions whereby these substrates are affected by CYP2D6 and additional enzyme inhibitions at CYP3A4, CYP2C19, CYP2C9, or CYP1A2 through one and the same drug which is the "multi enzyme" inhibitor fluvoxamine **[37]**.

Clinically relevant data is known for aripiprazole when used in the presence of strong CYP2D6 and CYP3A4 inhibitors based on expected in vivo AUC increases calculated by PBPK model. The manufacturer based his dose adjustments on the PBPK model and recommends dose reductions by 75% **[6]**, which accords to an AUC value of 400% (whereby the computed AUC-PBPK value indeed is reported with 450%). The MDDI Calculator shows in the case of aripiprazole in combination with the strong CYP2D6 inhibitor paroxetine and with the very strong CYP3A4 inhibitor itraconazole a stronger super additive effect than the PBPK study predicts, which leads to a deviation between MDDI value and study data (PBPK calculation), and with the "weaker" strong CYP3A4 inhibitor clarithromycin a very well matching AUCcomp of 400%, see **Table 4** and also chapter Discussion.

Table 4: Comparison of in vivo and computed data for multiple drug drug interactions of aripiprazole.

Substrate	Inhibitor	AUCcomp	AUCstudy	Deviation Factor	Literature
Aripiprazole	Paroxetine and Itraconazole	580%	400%-600% (PBPK)	104% (see discussion)	6,7
Aripiprazole	Paroxetine and Clarithromycin	400%	400% (PBPK)	100%	6,7

For tamsulosin, galantamine and vortioxetine in vivo data for concurrent inhibition of two metabolizing enzymes is not available from literature. The MDDI calculator can estimate a relative increase of AUC in combination therapies, which lead to inhibition of two or more metabolizing enzymes based on known kinetic properties of tamsulosin and calibration of pairwise drug interactions. Results are shown in **Table 5.**

A portion of 75% of Galantamine is metabolized by hepatic enzymes with the involvement of CYP2D6 and CYP3A4 **[33]**. Furthermore, it is eliminated renally. The AUC is expected to be nearly doubled in combination with ketoconazole and paroxetine **(Table 5).**

Tamsulosin is mainly metabolized by CYP3A4 with lesser contribution of CYP2D6, less than 10% are eliminated in urine unchanged **[34]**. Thus, the inhibition of both, CYP2D6 and CYP3A4 is expected to cause a strong super additive effect of AUC increase **(Table 5).**

Vortioxetine is metabolized by several cytochrome P450 enzymes, especially CYP2D6, furthermore CYP3A4/5, CYP2C9, and to minor extent by CYP2C19, CYP2A6, CYP2C8 and CYP2B6; CYP2D6 is the major metabolizing enzyme **[36]**. Significant AUC changes of pairwise drug interactions are reported for vortioxetine in combination

with the strong CYP3A4 and weak CYP2C8 inhibitor ketoconazole, the strong CYP2D6 inhibitor bupropion and the moderate CYP3A4 and strong CYP2C9 inhibitor fluconazole. In three way combination of the drugs the MDDI calculator shows highly different results, which are based on the substrate as well on the inhibitor properties which were adjusted by pairwise interactions. Both, bupropion and paroxetine are strong CYP2D6 inhibitors, which inhibit CYP2D6 in similar extent. Ketoconazole and fluconazole are inhibiting two different types of less important CYP2C enzymes as described above, but CYP2C9 is involved in the vortioxetine metabolism in higher extent than CYP2C8. Thus, inhibition of CYP2D6 and CYP3A4, especially when enhanced at CYP2C9, is expected to cause strong super additive effects of AUC increases (**[34-36]**, **Table 5**).

Table 5: Computed data for multiple drug drug interactions of galantamine, tamsulosin and vortioxetine

Substrate	Inhibitor	Invovled enzymes (blocked enzymes bold)	AUCcomp
Galantamine	Paroxetine and Ketoconazole	**CYP2D6, CYP3A4** and others, renal elimination	206%
Tamsulosin	Paroxetine and Ketoconazole	CYP2D6, CYP3A4	1090%
Vortioxetine	Bupropion and Ketoconazole	**CYP2D6, CYP3A4/5,** CYP2C9, CYP2C19, CYP2A6, **CYP2C8** and CYP2B6	459%
Vortioxetine	Paroxetine and Fluconazole	**CYP2D6, CYP3A4/5, CYP2C9,** CYP2C19, CYP2A6, CYP2C8 and CYP2B6	876%

Statistical analysis

A statistical analysis was performed for the 51 traditional pairwise drug drug interactions listed in **Table 2**; the number of Multiple Drug Drug Interactions (MDDI) was too limited to conduct a separate statistic analysis.

Student t-Test

Table 6: summary of Student t-test of $AUC_{comp,rel}$.

Value	Result
Number records	51
Average value $AUC_{comp,rel}$	99.45%
Variance $AUC_{comp,rel}$	0.17%
Standard deviation $AUC_{comp,rel}$	4.1%
Standard error $AUC_{comp,rel}$	0.57%
95% Confidence Interval $AUC_{comp,rel}$	98.3%//100.6%[1]

Average value $AUC_{study,rel}$	100%
Variance $AUC_{study,rel}$	0
Standard deviation $AUC_{study,rel}$	0
Standard error $AUC_{study,rel}$	0
95% Confidence Interval $AUC_{study,rel}$	n.a.[2]

[1]The 95% confidence interval for the two tailed one sample Student t-test with f = 50 = (51-1) and p = 0.05 is (98.3%; 100.6%) ⇔Average Value +- 2-fold Standard error (99.45% +- 0.57% * 2.01), and it falls within the set boundaries of 100% +- 24%; H_0 cannot be rejected therefore and AUC_{comp} and AUC_{study} are regarded to be equal.

[2]data is constant

Discussion

The target of this contribution was to show that a software and database search engine (MDDI Calculator) may be adjusted to assess and predict changes due to pharmacokinetic impacts in consistency with in vivo study data. Data comparison was done looking at traditional pairwise drug drug interactions and at multiple drug drug interactions, where one drug is affected through morefold interaction mechanisms and one or more other drugs at once. The focus was on the AUC changes of drugs, which predominantly are metabolized by the cytochrome P450 enzyme CYP2D6 combined with strong CYP2D6 inhibitors or administered in patients with poor metabolizer status because these scenarios help to assess SMPR values of substrates and may especially cause enhanced effects and possibly toxicity. Data of concrete AUC changes, which is normally gained from phase I clinical trials or case reports, is rare and for multiple drug drug interactions is extremely rare. But people get older and polypharmacy with 5, 6, or more drugs is widely spread in industrial countries. Assuming only 500 active ingredients, a number well in accordance with the number of active principles in SDB **[38]**, represent the bulk of medications, doctors may compile billions of different prescription combinations when prescribing polypharmacy. Nobody can make and finance research on all these combinations and their outcome. This shows the necessity of easily and quickly available information to assist doctors and pharmacists in the evaluation of kinetic drug interactions in clinical practice, especially in patients with polypharmacy and the risk of multi drug drug interactions.

Favatella et al. **[39]** state in this context in an apixaban related publication "Not all possible combinations of therapies can be formally tested" and "even with the extensive controlled trial evidence available on the use of apixaban in patients who are receiving potentially interacting medications, data do not exist to inform on all decisions that clinicians and patients must make. Through extrapolation of the class effect, the available summarized data can be used to estimate the impact of unstudied DDIs based on their PK properties."

PBPK models have been developed in recent years, but very detailed and chemical properties of each drug must be known to drive these calculations and time requirements are extremely big as stated in a PBPK related study by Luecht et al. **[40]** which focused also on a comparison of the PBPK-PK-Sim® and the SCHOLZ DataBank MDDI method when researching the multiple DDI of venlafaxine – bupropion - itraconazole. Thus, PBPK calculations are very helpful in drug development and drug sciences, but they are not suitable for the use in clinical practice. Moreover, this comparison showed that PBPK and MDDI can be on a par and MDDI may perform even better, if

the PBPK settings are not on the point. The final conclusion was: "The MDDI Calculator demonstrated good consistency with in vivo drug exposure data in the multiple interaction scenario of VEN–BUP–ITRA. Overall, the MDDI Calculator is a helpful tool that can be used to predict the effect of several inhibitors of CYP enzymes on the exposure of a substrate. Both PBPK and MDDI Calculator provide, in their own way, valuable tools to predict the DDI's extent."

The use of relative AUC changes for the calculation of dose adjustments or the determination of contraindications is a well established method used in the official prescribing information as well. The relative AUC data in the prescribing information is commonly accepted as the judicial scaffolding for healthcare professionals in clinical practice. Healthcare professionals are using these data for years to perform dose adaptions and risk minimization in drug therapy. This fact shows that the comparison of relative AUC changes is commonly suitable, so that relative AUC data from the literature, in case also from prescribing information, can be used well for the calibration of the MDDI calculator. All dose adaptions have to be performed carefully by healthcare professionals with considering interindividual differences and patient monitoring.

Apart from that, more study values, especially for multiple interactions, could help to verify and specify MDDI calculations. But due to the clinical risk of MDDI, systematic clinical trials are ethically critical, and can, as already mentioned, due to the immense financial implications, barely conducted in a satisfying manner. As long as no more data is available, actual MDDI calculations are one of the best approaches for clinicians to get kinetic information for evaluation of interactions and determination of dose adjustments in clinical practice at the point of care.

The comparison of the computed values of the MDDI Calculator shows for 51 pairwise DDIs measured in vivo excellent consistency; given the size of the sample this consistency could be backed up by applying statistical tests such as applying t-test analysis statistics. This accordance could be achieved by assigning to both the substrates and the inhibitors specific unique values for SMPR and MEC using a %-scale of their propensity to be metabolized by or to block the CYP2D6 metabolizing enzyme. The rational of this method is backed up especially by the fact that high consistency of parameters SMPR and MEC and AUC comparison results could be shown when looking at metoprolol, desipramine, or tamsulosine, all substrates with different SMPR values, impacted by inhibitors of different inhibitor strengths causing different MEC values for inhibitors such as paroxetine or mirabegron. One discrepancy from that ruling was detected in the sample: venlafaxine which is usually classified as a moderate inhibitor of CYP2D6 showed in vivo a stronger impact on the haloperidol exposure than the strong CYP2D6 blocker paroxetine and therefore needed a computational ruling of exemption: as C_{max} was increased by 88% and AUC by 70% with no impact on the haloperidol half time **[63]** it was concluded that venlafaxine might have an impact reducing the First Pass effect and thereby elevate the AUC; accordingly a placeholder transporter/enzyme inhibited by venlafaxine was introduced and the question if haloperidol bioavailability depends on such transporter/enzyme including CYP2D6 activity should be explored by further research; another interpretation could be based on a competition of venlafaxine and haloperidol at gastrointestinal CYP3A4. These findings support the potential role of the MDDI Calculator to hint to niches where more research is needed.

Another sort of discrepancy attracted attention as mirabegron which is usually classified as a moderate CYP2D6 inhibitor behaved nearly as strong as paroxetine affecting metoprolol as well as tamsulosin. The conclusion out of

these observations might be that mirabegron is concerning CYP2D6 in vivo indeed more in the strong inhibitor ballpark or other effects not yet recognized are of relevance, for example impacts through other CYP enzymes or changes in bioavailability. The latter mechanism could also play a role in the haloperidol venlafaxine case as the half time of haloperidol is reported not to be affected in this interaction.

Dose recommendations for aripiprazole in combination with strong CYP3A4 and CYP2D6 inhibitors come from PKPB Modeling. In this context, strong inhibitors are seen as one homogenous group of drugs, but in reality, the drugs, which are named 'strong inhibitors' are considerably different. The dose recommended for dose adjustment with contemporary use of strong CYP3A4 and strong CYP2D6 inhibitors is 75% lower than normal dose. This matches accurately the case of clarithromycin causing Kel_{rel} = 25% but only practically the case of itraconazole with Kel_{rel} = 17%. As the tablets may be quartered, both dose recommendations will lead to the same dose adjustment in clinical practice. Of course, all dose adjustments must be performed carefully with patient monitoring. However, as the potency to inhibit CYP3A4 of inhibitors such as ketoconazole or itraconazole or clarithromycin is actually rather different as the impact of the azols causes an AUC increase for the sensitive CYP3A4 substrate simvastatin to the 18-fold **[64]** whereas the clarithromycin achieves only the 10-fold **[65]**, it has to be assumed, that an in vivo study of the triple interaction "aripiprazole – paroxetine – itraconazole" would probably demonstrate a substantially higher AUC value for aripiprazole than the PBPK method indicates. When the CYP2D6 is blocked completely halving the metabolism of aripiprazole, then about 2/3 of the remaining metabolizing capacity is controlled by liver CYP3A4. If the blocking impact of clarithromycin on liver CYP3A4 yields another halving of the metabolism according to Kel_{rel} = 25% and AUC_{rel} = 400% whereby its effect is substantially weaker than the practically complete inhibition by itraconazole the latter should cause in total an AUC_{rel} in the range of 600%. The MDDI Calculator computes actually a Kel_{rel} = 17% and an AUC_{rel} of 580% and is thereby in line with the Prescriber Information quoted which expects in CYP2D6 poor metabolizers a 3-fold AUC increase when a strong CYP3A4 inhibitor is administered. Insofar some ambiguity lies evidently in this Prescriber Information and the "true" value for the AUC increase in the case of complete CYP2D6 inhibition (by drug or genetically) plus strong or strongest CYP3A4 inhibition may be located in the range of the 4 – 6-fold.

The 5 multiple DDIs caused by fluvoxamine deserve special attention. Clozapine **[20,31]**, imipramine **[14,31,42,43]**, pirfenidone **[41]**, risperidone **[14,31]**, and thioridazine **[14,31,44]** and their metabolisms are all dependent on 2 and more enyzmes including CYP2D6. Fluvoxamine is a strong inhibitor of CYP1A2 and CYP2C19, a moderate inhibitor of CYP2C9 and CYP3A4 and a weak inhibitor of CYP2D6 **[20,37]**. First of all, these 5 AUC_{comp} assessments made showed high consistency with deviations from in vivo study values of less than 10% although enzyme scenarios involved are quite different whereby similar to the haloperidol – venlafaxine case an additional impact of fluvoxamine on CYP2D6 controlled bioavailability of substrates was assumed. Furthermore it has been demonstrated that it does not matter if multiple enzyme/transporter inhibitions are caused by only one or multiple drugs and that multiple effects including minor contributions can result in clinically significant DDI and MDDI respectively as pointed out by Isoherranen et al., too **[8]**. Clinicians should be aware that inhibitors such as fluvoxamine or combinations of inhibitors affecting different enzymes substantially may cause "multi enzyme

failure" and consequently seriously elevated plasma levels of substrates, especially of those with narrow therapeutic index.

The MDDI Calculator uses for its assessments of drug exposure changes a complex system of multidimensional Dettli type formulas **[66-68]** to compute Kel_{rel} (instead of the individual elimination fraction Q) supplemented by a similar term for the assessment of F_{rel} dependent on the extent FP is affected by transporter inhibitions. The precise functioning is a trade secret of SCHOLZ DataBank, Inc. **[13]**. The Dettli formula has proven itself for decades as reliable tool to compute drug dose adjustments needed due to renal failure and looks therefore, and because of the very similar logic of assessing Kel_{rel} due to DDIs and MDDIs, to be a very appropriate platform to be applied in an expanded multidimensional format for the assessment of Kel_{rel} able to reconcile kinetic drug interactions, patient individual data related to renal stage and also pharmacogenetic properties, as enzyme/transporter inhibition by drugs resulting in DDI or MDDI may mimick consequences in drug metabolism through pharmacogenetics such as PM or IM. A contribution by the author was recently published questioning if the Dettli formula needs an update moving away from linearity, for example in the case of metformin **[45]**. Due to the fact that non linearity in Michaelis-Menten kinetics may occur occasionally when effective drug therapy can only be supported with drug concentrations in the range or higher than the Michaelis constant Km as known in the case of phenytoin **[46]** more research related to scenarios with floating K_{el} due to enzyme/transporter saturation is required.

A last remark shall be dedicated to how the MDDI Calculator is related to AI. First of all automated and learning procedures help to accelerate furthermore the refining of drug properties and to improve the precision in respect to consistency with in vivo clinical data, dose dependent phenomena, and reconciliation with pharmacodynamic effects and adverse drug reactions. The target of minimizing the sum of all deviations of computed and measured data will be accomplished most effectively, too. The refinement process is already rather advanced and MDDI meaningful knowledge for about 700 active ingredients, substrates and inhibitors of relevance in this matter, and their drugs is now available and is steadily supplemented. Therefore the MDDI Calculator is ready to validate its predictive power in everyday clinical decision support in practice or care management when identifying and avoiding potentially dangerous drug combinations. However, this may require comprehensive time consuming and expensive case investigations including drug plasma level measurements or Drug Utilization Reviews (DUR) including the evaluation of adverse reactions, especially looking at patients on polypharmacy. Alternatively, to save time and money, Dr. Random's Drug Interaction Clock of SDB has been developed in an AI oriented initiative which can be used to screen in a mass data analysis within days hundred thousands to millions prescriptions which are compiled in 5 to 12-drug samples either randomly, or targeted based on guideline recommended scenarios, or according to real patient data. Thus potentially dangerous scenarios where in particular MDDI caused elevated plasma levels and narrow therapeutic indices meet can be detected, compiled in the Polypharmacy Library of SCHOLZ DataBank, and commented by Health Care Professionals. This approach can be also helpful before or when introducing a new drug to gain more insights into potential hazards resulting from unknown combo therapies with the new drug. Last but not least, all kinetic interactions detected by the MDDI Calculator have to be reconciled with the adverse reactions caused possibly thereby. To reveal these dependencies including impacts by dosing, renal failure stages and pharmacogenetics more sophisticated software, AI software, is needed. The Adverse Drug Risk Control Panel (ADR

CP) of SCHOLZ DataBank with its Medication Optimizer has an answer to these challenges, too, and how to avoid increased risks of severe bleeding by apixaban or Acute Kidney Injury (AKI) by rosuvastatin was recently published demonstrating the capability to find and optimize also hidden and dose dependent drugs risks in drug interaction scenarios **[69,70]**. The importance to develop AI based drug decision support systems with Optimizer functions has to be emphasized, in particular, as the annual costs of drug related morbidity and mortality in 2016 resulting from nonoptimized medication therapy were estimated to amount to $528.4 billion in the U.S. according to a study published by Watanabe et al. **[71]**.

Conclusion

In total, based on 51 drug drug interactions evaluated, it can be concluded that the MDDI Calculator is able to compute changes of drug exposure in pairwise kinetic DDIs in a very reliable and excellent manner; it can be assumed that exemption ruling as needed in the haloperidol venlafaxine case would not be necessary if the background of that interaction would be completely known and understood. The MDDI Calculator in so far turns out also as an instrument providing effective support to detect fields of drug drug interactions which need further research and exploration. Furthermore, based on the property settings of ingredients according to the available pairwise in vivo data, the AUC changes for multiple pharmacokinetic drug drug interactions (MDDI) may be predicted, too. The predictive power of the MDDI calculator for multiple drug drug interactions is very well confirmed when looking at the few multiple drug drug interactions where in vivo data is available. Regarding in summary all 51 pairwise and 3 triple drug drug interactions researched, the AUC values, in all cases assessed with less than +- 10% deviation from in vivo data, surpassed substantially the set “excellency” target range of 100% +- 24%.

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