The mechanistic evaluation of enzyme- and transporter-based drug-drug interactions (DDIs) during drug development is critical to support management strategies in clinical settings. The mechanism(s) and clinical relevance of these interactions were characterized based on information available in the NDA reviews. DDIs were identified from clinical trials, pharmacogenetics studies, pharmacokinetics (PKB) modeling and simulations, and population PK analyses. Positive study results (>140 studies), defined as mean area under the curve (AUC) ≥ 1.25 for inhibition DDIs or pharmacogenetics studies and ≥ 0.8 for induction DDIs, were fully analyzed.

Results: When new drugs were evaluated as victims of enzyme-based DDIs, a total of 18 drugs (50%) had positive study results with inhibition of CYP enzyme explaining most of the observed interactions (>85%). Six drugs, namely atorvastatin, fenerone, bexafos, irifinitin, methylcob, and voricon, were found to be sensitive substrates of CYP3A, with AUCRs of 5.45-16.55 with co-administered drugs with the strong inhibitors iraconazole or ketoconazole. Of note, all of them were also substrates of P-gp in vitro, confirming the strong overlap between CYP and P-gp. Avancan and belzutan were found to be moderate sensitive substrates (AUCRs 2.5) of CYP3A and UGT2B7, respectively. Regarding transporters, only two drugs, atorvastatin (P-gp and OCT2B183) and zileuton (OCT2B183), were clinical substrates of transporters, with a maximum AUC of 2.85 for atorvastatin after single dose rifampin administration due to inhibition of OCT2B183. As perpetrators, only one drug, viloxazine, was considered a strong inhibitor of CYP2A12 (caffeine AUCR 5.83). No drug exhibited strong inhibition of transporters. The following drugs were found to be moderate inhibitors: atorvastatin (CYP3A4), bexafos, irifinitin (CYP3A and CYP2C19), and bexafos, irifinitin (OCT2B183). No strong inducers of enzymes or transporters were identified. All DDIs with an AUCR ≥ 5 and most of DDIs with an AUCR ≥ 2 fold and most moderate DDIs led to label recommendations to mitigate the risk of DDI in clinical settings.

NMEs as substrates:
- There were 81 positive interaction studies where NMEs were the substrates (or victim drugs). Inhibition and induction of cytochrome P450 (CYP) 3A4 explained most (>85%) of these interactions.
- Based on the results of mechanistic studies with clinical index inhibitors, 6 drugs were identified as sensitive substrates of CYP3A: atorvastatin, fenerone, bexafos, irifinitin, methylcob, and voricon. (Table 1). Of note, all of them were also substrates of P-glycoprotein (P-gp) in vitro, confirming the strong overlap between CYP and P-gp.
- Two drugs were found to be moderate sensitive substrates (AUCRs 2.5) based on inhibition or pharmacometric results: avancan (CYP3A) and delafuzin (UGD-glucuronosyltransferase (UGT) 2B17).
- Regarding transporters, atorvastatin (P-gp and organic anion transporting polypeptide (OATP) 1B1/183) and zileuton (OCT2B183), were found to be clinical substrates of transporters, with a maximum AUC of 2.85 for atorvastatin following single dose rifampin administration due to inhibition of OCT2B183.
- All DDIs with an AUC ≥ 5 and most of DDIs with an AUC 2.5 led to specific label recommendations when NMEs are concomitantly administered with known inhibitors or inducers, while for DDIs with an AUC < 2, less than a third led to clinical recommendations.

Conclusions: Understanding the mechanisms and clinical extent of DDIs with these newly approved drugs will certainly help guide DDI management strategies in patient populations who often receive polypharmacy.

METHODS

The University of Washington Drug Interaction Database (www.druginteractionolutions.org) was used to identify clinical DDI studies available for drugs approved by the FDA in 2021.

The mechanism(s) and clinical relevance of these interactions were characterized based on information available in the NDA reviews. DDI study results from dedicated DDI clinical trials, pharmacogenetics studies, as well as PKB modeling and simulations that functioned as alternatives to dedicated clinical studies were examined.

Using available mean area under the time- plasma concentration curve ratios (AUCRs), all clinical studies with AUCRs ≥ 2.25 and 0.8 (i.e. positive DDI results) were fully analyzed.

Applying the categorization recommended by the FDA, any drug interactions with AUC changes ≥ 5-fold (9, AUC > 5 or 0.2; 2-5-fold (≥ AUC > 5 or 0.2 AUC > 0.8) or 2-0.25-1-fold (≥ 0.2 AUC > 2 or 0.25-0.5 AUC ≥ 0.8) were considered strong, moderate, or weak drug interactions, respectively.

Results

To review pharmacokinetic-based clinical DDI data available in the new drug application (NDA) reviews for drugs approved by the FDA in 2021.

To understand main mechanisms that mediate interaction results in label recommendations.

NMEs as precipitants:
- There were 56 positive interaction studies where NMEs were inhibitors or inducers. Only 8 moderate or strong drug interactions involving 6 drugs were observed, including 7 moderate or strong inhibition interactions and 1 moderate induction interaction.
- Only one drug, viloxazine, was considered a strong inhibitor of CYP2A12 (caffeine AUCR 5.83) (Table 1). No drug exhibited strong inhibition of transporters.
- Four drugs were found to be moderate inhibitors (AUCRs 2.5): atorvastatin (CYP3A), bexafos, irifinitin (CYP3A), fenerone (CYP3A), and zileuton (OCT2B183).
- No strong induction of enzymes was observed. No drugs were identified as transporter inducers.
- Four drugs showed weak or moderate induction (AUCR 0.5-2.5) of enzymes, with atorvastatin showing the maximum induction and considered a moderate inducer of CYP3A (midazolam AUCR 0.47).
- Similarly to DDIs as substrates, most strong and moderate interactions led to label recommendations to mitigate the risk of DDI in clinical settings.
- A third of the weak interactions were mediated by drug transporters, involving P-gp, organic anion transporter (OAT) 1 and 3, organic cation transporter (OCT) 2, and multidrug and toxic compound extruder (MATE) 1 and 3. Half of the weak interactions were considered clinically relevant and led to clinical recommendations.

Conclusions

The present analysis evaluated the mechanisms involved in pharmacokinetic-based clinical drug interactions involving drugs approved by FDA in 2021, with a focus on those triggering label recommendations.

As victims of DDIs:
- Inhibition and induction of CYP3A explained most of all observed clinical interactions.
- Six drugs, namely atorvastatin, fenerone, bexafos, irifinitin, methylcob, and voricon, were found to be sensitive substrates of CYP3A.
- Avancan and belzutan were found to be moderate sensitive substrates of CYP3A and UGT2B7, respectively.
- Atorvastatin (P-gp and OCT2B183) and zileuton (OCT2B183) were clinical substrates of transporters.

As precipitants of DDIs:
- Only one drug, viloxazine, was considered a strong inhibitor of CYP2A12, and no drug showed strong inhibition of transporters.
- Four drugs were found to be moderate inhibitors: atorvastatin (CYP3A), bexafos, irifinitin (CYP3A), and zileuton (OCT2B183).
- No strong inducer of enzymes or transporters was identified. Sorbitol exhibited the most significant induction and was considered a moderate inducer of CYP3A.

All DDIs with AUC changes ≥ 5-fold and most DDIs with AUC changes 2- to 5-fold triggered dosing recommendations.