P56. ENZYME- AND TRANSPORTER-MEDIATED CLINICAL DRUG INTERACTIONS WITH DRUGS APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION IN 2021: WHAT CAN BE LEARNED FROM NEW DRUG APPLICATION REVIEWS?

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ABSTRACT

The mechanistic evaluation of enzyme- and transporter-based drug-drug interactions (DDIs) during drug development is critical to support management strategies in the clinic.

Methods: In the present work, DDI data for small molecular drugs approved by the U.S. Food and Drug Administration in 2021 (N = 36) were analyzed using the University of Washington Drug Interaction Database. The mechanism(s) and clinical magnitude of these interactions were characterized based on information available in the new drug application reviews. DDI data from dedicated clinical trials, pharmacogenetics studies, physiologically-based pharmacokinetics (PBPK) modeling and simulations, and population PK analyses were examined. Positive study results (~140 studies), defined as mean area under the curve ratios (AUCRs) ≥ 1.25 for inhibition DDIs or pharmacogenetics studies and ≤ 0.8 for induction DDIs, were then fully analyzed.

Results: When new drugs were evaluated as victims of enzyme-based DDIs, a total of 18 drugs (50%) had positive results with inhibition and induction of CYP3A explaining most of the observed interactions (~85%). Six drugs, namely atogepant, finerenone, ibrexafungerp, infigratinib, mobocertinib, and voclosporin, were found to be sensitive substrates of CYP3A, with AUCRs of 5.45-18.55 when co-administered with the strong marker inhibitors itraconazole or ketoconazole. Of note, all of them were also substrates of P-gp *in vitro*, confirming the strong overlap between CYP3A and P-gp. Avacopan and belzutifan were found to be moderate sensitive substrates (AUCRs 2-5) of CYP3A and UGT2B17, respectively. Regarding transporters, only two drugs, atogepant (P-gp and OATP1B1/1B3) and odevixibat (P-gp), were clinical substrates of transporters, with a maximum AUCR of 2.85 for atogepant following single dose rifampin administration due to inhibition of OATP1B1/1B3. As perpetrators, only one drug, viloxazine, was considered a strong inhibitor of CYP1A2 (caffeine AUCR 5.83). No drug exhibited strong inhibition of transporters. The following drugs were found to be moderate inhibitors: asciminib (CYP2C9), belumosudil (CYP3A), fexinidazole (CYP1A2 and CYP2C19), and ibrexafungerp (OATP1B3). No strong inducer of enzymes or transporters was identified. Four drugs showed induction, with sotorasib showing the maximum induction and considered a moderate inducer of CYP3A (midazolam AUCR 0.47). As expected, all DDIs with AUCRs ≥ 5 or ≤ 0.2 (≥ 5-fold change) and almost all those with AUCRs of 2-5 and 0.2-0.5 (2- to 5-fold change) triggered dosing recommendations in the product labels. PBPK modeling and simulations continued to be increasingly used as alternatives to dedicated DDI clinical trials, with 10 drugs evaluated as victims and 5 drugs as inhibitors using in silico evaluations. Similar to drugs approved in recent years, oncology was the most represented therapeutic area, including 31% of 2021 approvals. However, drugs found to be either sensitive substrates or strong inhibitors of enzymes included treatments for a variety of diseases, e.g., antifungals, cancer treatments, central nervous system agents, depression treatments, and immune system agents.

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.

OBJECTIVES

- 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 interactions resulting in label recommendations.

METHODS

- The University of Washington Drug Interaction Database (www.druginteractionsolutions.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, pharmacogenetic studies, as well as PBPK 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 ≥ 1.25 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 (i.e., AUCRs ≥ 5 or ≤ 0.2), 2- to 5-fold (2 ≤ AUCR < 5 or 0.2 < AUCR ≤ 0.5), or 1.25- to 2-fold (1.25 ≤ AUCR < 2 or 0.5< AUCR ≤ 0.8) were considered strong, moderate, or weak drug interactions, respectively.

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Questions? *Please contact Dr. Jingjing Yu jingyu@uw.edu should you have any questions.*

RESULTS

Therapeutic classes

- A total of 36 small new molecular entities (NMEs) were approved by the FDA in 2021.
- Antineoplastic agents were found to be the most represented therapeutic area, comprising 31% of all approved drugs (Figure 1). Among the 11 oncology drugs, nine were kinase inhibitors, highlighting the continuous major role of this therapeutic class in cancer therapy.
- More than half of the drugs (N = 17; 63%) were considered first-in-class, a strong indicator of the continuous innovation of the pharmaceutical industry, and about two thirds (N = 19; 73%) of all drugs were approved under the orphan disease approval process.

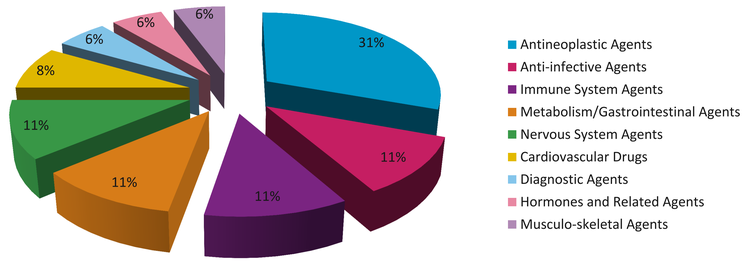

Figure 1. Therapeutic classes of drugs (small molecules) approved by the FDA in 2021

NMEs as substrates

- There were 81 positive interaction studies where NMEs were the substrates (or victim drugs). Inhibition and induction of cytochrome P450 (CYP) 3A 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: atogepant, finerenone, ibrexafungerp, infigratinib, mobocertinib, and voclosporin (Table 1). Of note, all of them were also substrates of P-glycoprotein (P-gp) *in vitro*, confirming the strong overlap between CYP3A and P-gp.
- Two drugs were found to be moderate sensitive substrates (AUCRs 2-5) based on inhibition or pharmacogenetic results: avacopan (CYP3A) and belzutifan (UDP-glucuronosyltransferase (UGT) 2B17)
- Regarding transporters, atogepant (P-gp and organic anion transporting polypeptide (OATP) 1B1/1B3) and odevixibat (P-gp), were found to be clinical substrates of transporters, with a maximum AUCR of 2.85 for atogepant following single dose rifampin administration due to inhibition of OATP1B1/1B3.
- All DDIs with an AUCR ≥ 5 and most of DDIs with an AUCR 2-5 led to specific label recommendations when NMEs are concomitantly administered with known inhibitors or inducers, while for DDIs with an AUCR < 2, less than a third led to clinical recommendations.

NMEs as precipitants

- There were 55 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 CYP1A2 (caffeine AUCR 5.83) (Table 1). No drug exhibited strong inhibition of transporters.
- Four drugs were found to be moderate inhibitors (AUCR 2-5): asciminib (CYP2C9), belumosudil (CYP3A), fexinidazole (CYP1A2 and CYP2C19), and ibrexafungerp (OATP1B3).
- No strong induction of enzymes was observed. No drugs were identified as transporter inducers.
- Four drugs showed weak or moderate induction (AUCR 0.5-0.8) of enzymes, with sotorasib 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 extrusion (MATE) 1 and 2-K. Half of the weak interactions were considered clinically relevant and led to clinical recommendations.

RESULTS

Table 1. Drug interactions with AUC changes ≥ 5-fold in the victim drugs

Substrate	Precipitant	NME Therapeutic Class	AUCR	Enzyme or Transporter Primarily Involved	Label Impact
inhibition DDIs with AUCRs ≥ 5, NMEs as substrates					
atogepant	itraconazole	Nervous System Agents	5.45	CYP3A4[a]	reduce dose with concomitant use of strong CYP3A4 inhibitors
finerenone	itraconazole	Cardiovascular Drugs	6.33[b]	CYP3A4[a]	contraindicated with strong CYP3A4 inhibitors
ibrexafungerp	ketoconazole	Anti-infective Agents	5.76	CYP3A[a]	reduce dose with concomitant use of a strong CYP3A inhibitor
infigratinib	itraconazole	Antineoplastic Agents	7.22	CYP3A[a]	avoid concomitant use with moderate or strong CYP3A inhibitors
mobocertinib	itraconazole	Antineoplastic Agents	8.42	CYP3A[a]	avoid concomitant use with strong CYP3A inhibitors
voclosporin	ketoconazole	Immune System Agents	18.55[c]	CYP3A4[a]	contraindicated with strong CYP3A4 inhibitors
induction DDIs with AUCRs ≤ 0.2, NMEs as substrates					
avacopan	rifampin	Immune System Agents	0.07	CYP3A4	avoid concomitant use with strong and moderate CYP3A4 inducers
finerenone	rifampin	Cardiovascular Drugs	0.07[b]	CYP3A4[a]	avoid concomitant use with strong and moderate CYP3A4 inducers
mobocertinib	rifampin	Antineoplastic Agents	0.04	CYP3A[a]	avoid concomitant use with strong CYP3A inducers
voclosporin	rifampin	Immune System Agents	0.13	CYP3A4[a]	avoid concomitant use with strong and moderate CYP3A4 inducers
inhibition DDIs with AUCRs ≥ 5, NMEs as precipitants					
caffeine	**viloxazine**	Nervous System Agents	5.83	CYP1A2	contraindicated with sensitive or NTI CYP1A2 substrates; not recommended with moderate sensitive CYP1A2 substrates, if co-administered, dose reduction of the CYP1A2 substrate may be warranted

Maximum AUCR is presented for the same mechanism; NMEs are bolded; for each section, DDIs are arranged alphabetically; all the studies were performed in healthy volunteers and all drugs were administered orally; for the enzyme CYP3A, to be consistent with the drug label, either CYP3A or CYP3A4 is used; NTI, narrow therapeutic index

[a] *In vitro*, the NME was a substrate of P-gp. Inhibition or induction of P-gp may also have contributed to the NME exposure change.

[b] The result was obtained from PBPK analysis

[c] $AUC_{0\text{-}12h}$

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 atogepant, finerenone, ibrexafungerp, infigratinib, mobocertinib, and voclosporin were identified to be sensitive substrates of CYP3A.
- Avacopan and belzutifan were found to be moderate sensitive substrates of CYP3A and UGT2B17, respectively.
- Atogepant (P-gp and OATP1B1/1B3) and odevixibat (P-gp) were clinical substrates of transporters.

As precipitants of DDIs:

- Only one drug, viloxazine, was considered a strong inhibitor of CYP1A2, and no drug showed strong inhibition of transporters.
- Four drugs were found to be moderate inhibitors: asciminib (CYP2C9), belumosudil (CYP3A), fexinidazole (CYP1A2 and CYP2C19), and ibrexafungerp (OATP1B3)
- No strong inducer of enzymes or transporters was identified. Sotorasib 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.

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