MAIN MECHANISMS OF PHARMACOKINETIC DRUG-DRUG INTERACTIONS TRIGGERING LABEL RECOMMENDATIONS FOR DRUGS APPROVED BY THE FOOD AND DRUG ADMINISTRATION IN 2018

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ABSTRACT

The aim of the present work was to review pharmacokinetic drug-drug interaction (DDI) data available in New Drug Applications (NDAs) for drugs approved by the US Food and Drug Administration in 2018 and analyze the mechanisms mediating interactions that triggered label recommendations.

Methods: The University of Washington Metabolism and Transport Drug Interaction Database® was used to identify clinical DDI studies available in the NDAs, and interactions resulting in label recommendations due to safety concerns (from contraindication to simple monitoring for adverse reactions) were further evaluated.

Results: For the 42 new molecular entities (NMEs) approved in 2018, 22 (52%) drugs - including 11 antineoplastic agents - had label recommendations based on the results of DDI evaluations (clinical trials or physiologically-based pharmacokinetic [PBPK] modeling and simulations). Interestingly, 41% of interactions triggering label recommendations had changes in victim area under the curve (AUC) below 2-fold, suggesting a fairly narrow therapeutic index for said victim drugs. CYP3A was the predominant enzyme, involved in a large majority (72%) of all interactions. Fourteen drugs were found to be substrates of CYP3A, with AUC ratios (AUCR) ≥ 1.25 or ≤ 0.8 when co-administered with a strong CYP3A inhibitor or inducer, respectively. While none of them presented an AUCR ≥ 5 in the presence of a strong CYP3A inhibitor, five drugs, namely doravirine, duvelisib, larotrectinib, lorlatinib, and netupitant [the active moiety of the prodrug fosnetupitant], exhibited high sensitivity to induction, with exposure decreases of 80-88% when co-administered with the strong inducer rifampin. When NMEs were evaluated as perpetrators of enzymes, dacomitinib was found to be a strong inhibitor of CYP2D6 (dextromethorphan AUCR 9.55), apalutamide a strong inducer of CYP3A (midazolam AUCR 0.08) and CYP2C19 (omeprazole AUCR 0.15), and ivosidenib a strong CYP3A inducer (midazolam AUCR 0.10). For transporters, P-gp was the transporter most often identified and among the 14 NMEs metabolized by CYP3A, 11 were found to also be substrates of P-gp *in vitro*. The gonadotropin-releasing hormone antagonist elagolix exhibited the highest change in exposure due to transporter inhibition, with a single oral dose of rifampin significantly increasing its exposure 5.58-fold, suggesting that elagolix is a sensitive substrate of OATP1B1. When NMEs were considered as perpetrators, all transporter-mediated interactions observed were weak inhibitions (AUCR < 2), with six drugs found to be weak inhibitors of P-gp, BCRP, OATP1B1/1B3, OCT2, and/or MATE1.

Conclusion: Inhibition and induction of CYP3A were the most common mechanisms observed in clinical interactions triggering dosing recommendations. Most transporter-mediated interactions had a limited magnitude of exposure change except for elagolix, which was identified as a sensitive substrate of OATP1B1.

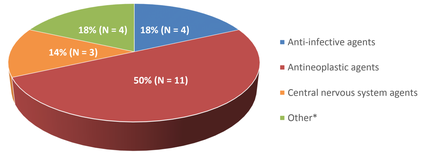
OBJECTIVES

- To review pharmacokinetic-based clinical DDI data available in the NDA reviews for drugs approved in 2018.
- To understand main mechanisms that mediate interactions resulting in label recommendations.

RESULTS

- For the 42 NMEs (small molecules) approved in 2018, 22 (52%) drugs - including 11 antineoplastic agents - had label recommendations based on the results of DDI evaluations from clinical trials or PBPK modeling and simulations (Figure 1).
- Interestingly, 41% of interactions triggering label recommendations had changes in victim AUC below 2-fold, suggesting a fairly narrow therapeutic index for said victim drugs.

Figure 1. Therapeutic classes of drugs (N = 22) with label recommendations.

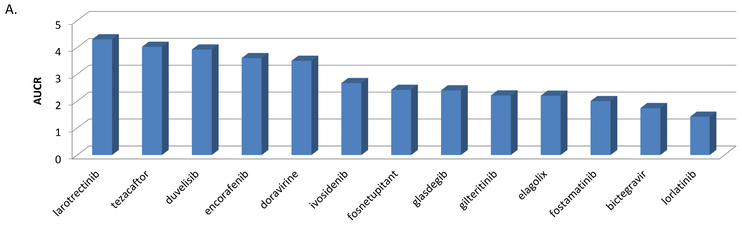


*Includes Antihemorrhagics/hemostatics, Gastrointestinal agents, Respiratory system products, and Treatment of pain and inflammation

Metabolism-Based DDI: NMEs as Substrates

- CYP3A was the predominant enzyme involved in a large majority (72%) of all interactions. Fourteen drugs were found to be substrates of CYP3A, with AUCR ≥ 1.25 or ≤ 0.8 when co-administered with a strong CYP3A inhibitor or inducer, respectively (Figure 2).
- No drugs presented an AUCR ≥ 5 in the presence of a strong CYP3A inhibitor; however, five drugs, namely doravirine, duvelisib, larotrectinib, lorlatinib, and netupitant (the active moiety of the prodrug fosnetupitant) exhibited high sensitivity to induction with exposure decreases of 80-88% when co-administered with the strong inducer rifampin.
- Other enzymes, CYP2C8, CYP2D6, and UGT1A1, mediated the inhibition interactions of four drugs (Table 1).

A.



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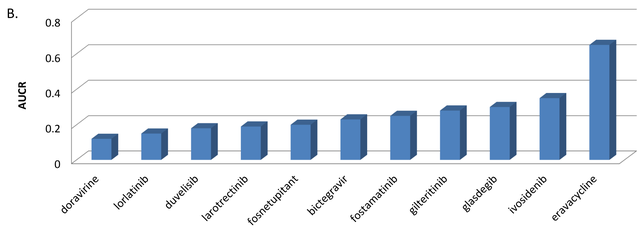

Figure 2. CYP3A-mediated inhibition DDIs (inhibitors include darunavir, itraconnaozle, ketoconazole, posaconazole, and ritonavir) (A) and induction DDIs (rifampin as the inducer) (B) with label recommendations.

Table 1. Metabolism-based inhibition DDIs mediated by other enzymes, NMEs as substrates

Substrate	Inhibitor	AUCR	Enzyme	Label Impact
apalutamide	gemfibrozil	1.53	CYP2C8	Consider dose reduction with a strong CYP2C8 inhibitor.
bictegravir	atazanavir	4.14	UGT1A1, CYP3A	Not recommended with other HIV anti-retrovirals that are strong CYP3A inhibitors and also UGT1A1 inhibitors.
dacomitinib	paroxetine	1.37	CYP2D6	None.
lofexidine	paroxetine	1.30	CYP2D6	Monitor for orthostatic hypotension and bradycardia with a CYP2D6 inhibitor.

Metabolism-Based DDIs: NMEs as Inhibitors

- Seven drugs were found to be inhibitors of enzymes (mainly CYP3A) (Table 2).
- Dacomitinib was a strong inhibitor of CYP2D6 (AUCR 9.55, dextromethorphan).

Table 2. Metabolism-based inhibition DDIs, NMEs as inhibitors

Inhibitor	Substrate	AUCR	Enzyme	Label Impact
dacomitinib	dextromethorphan	9.55	CYP2D6	Avoid CYP2D6 substrates.
duvelisib	midazolam	4.33	CYP3A	Monitor for toxicities associated with sensitive CYP3A substrates.
cannabidiol	clobazam	2.64-3.38 (norclobazam); 1.21	CYP2C19, CYP3A, CYP2B6	Reduce dose of clobazam.
fosnetupitant	midazolam	2.44	CYP3A	Caution with CYP3A4 substrates; avoid CYP3A4 substrates for one week, if not, reduce dose.
cannabidiol	midazolam	2.11 (1'-OH mdz); 0.94	UGT2B7	Reduce dose of UGT2B7 substrates.
larotrectinib	midazolam	1.70; 1.40 (1'-OH mdz)	CYP3A, UGTs	Avoid sensitive CYP3A4 substrates, if not, monitor for AEs.
fostamatinib	simvastatin	1.64	CYP3A	Monitor for toxicities of CYP3A4 substrate that may require dosage reduction.
tecovirimat	repaglinide	1.29	CYP2C8	Monitor blood glucose and hypoglycemic symptoms with repaglinide.
stiripentol	clobazam	Not provided	CYP3A, CYP2C19	Reduce dose of clobazam.

1'-OH mdz: 1'-hydroxy-midazolam.

Metabolism-Based DDIs: NMEs as Inducers

- Six drugs were found to be inducers of enzymes (mainly CYP3A) (Table 3).
- Apalutamide was a strong inducer of CYP3A (AUCR 0.08, midazolam) and CYP2C19 (AUCR 0.15, omeprazole) and also a weak inducer of CYP2C9; ivosidenib was a strong CYP3A inducer (AUCR 0.10, midazolam) and also a weak inducer of CYP2C9.

Table 3. Metabolism-based induction DDIs, NMEs as inducers

Inducer	Substrate	AUCR	Enzyme	Label Impact
apalutamide	midazolam	0.08	CYP3A	Substitute medications that are CYP3A substrates; if not, evaluate for loss of therapeutic effect.
ivosidenib	midazolam	0.10 (PBPK)	CYP3A	Avoid sensitive CYP3A substrates; if unavoidable, monitor for loss of therapeutic effect.
apalutamide	omeprazole	0.16	CYP2C19	Substitute medications that are CYP2C19 substrates; if not, evaluate for loss of therapeutic effect.
lorlatinib	midazolam	0.36	CYP3A	Avoid CYP3A substrates.
elagolix	midazolam	0.45	CYP3A	May decrease plasma concentrations of drugs that are substrates of CYP3A; increase dose of midazolam and individualize therapy.
encorafenib	midazolam	0.45	CYP3A	May decrease efficacy of sensitive CYP3A substrates.
apalutamide	(S)-warfarin	0.51	CYP2C9	Substitute medications that are CYP2C9 substrates; if not, evaluate for loss of activity.
tecovirimat	midazolam	0.68	CYP3A	Monitor for effectiveness of midazolam.
ivosidenib	(S)-warfarin	0.77 (PBPK)	CYP2C9	Use alternative therapies that are not sensitive substrates of CYP2C9; if unavoidable, monitor for loss of therapeutic effect.

Transporter-Based DDIs: NMEs as Substrates

- Three drug interactions with label recommendations were mediated mainly by transporters, including OATP1B1, OAT3, and P-gp (Table 4).
- Elagolix was found to be a sensitive substrate of OATP1B1, with an AUCR of 5.58 in the presence of rifampin.

Table 4. Transporter-based inhibition DDIs, NMEs as substrates

Substrate	Precipitant	AUCR	Transporter	Label Impact
elagolix	rifampin	5.58	OATP1B1	Contraindicated with strong OATP1B1 inhibitors.
baricitinib	probenecid	2.03	OAT3	Not recommended with strong OAT3 inhibitors.
talazoparib	P-gp inhibitors[1]	1.45 (popPK)	P-gp	Reduce the dose of talazoparib with any of these P-gp inhibitors.

[1]P-gp inhibitors include amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil.

Transporter-Based DDIs: NMEs as Inhibitors

- Four drugs were found to be inhibitors of transporters, including P-gp, BCRP, OCT2, and MATE1 (Table 5).
- No strong or moderate inhibitors were identified.
- Fostamatinib showed the highest AUCR of 1.96 in rosuvastatin due to BCRP inhibition.

Table 5. Transporter-based inhibition DDIs, NMEs as inhibitors

Inhibitor	Substrate	AUCR	Transporter	Label Impact
fostamatinib	rosuvastatin	1.96	BCRP	Monitor for toxicities of BCRP substrate drugs that may require dosage reduction.
bictegravir	metformin	1.39	OCT2, MATE1	May increase plasma concentrations of drugs that are OCT2 or MATE substrates; refer to metformin label for assessing the benefit and risk of concomitant use; contraindicated with dofetilide.
fostamatinib	digoxin	1.37	P-gp	Monitor for toxicities of P-gp substrate drugs that may require dosage reduction.
tezcaftor/ ivacaftor[1]	digoxin	1.30	P-gp	Caution and appropriate monitoring should be used with digoxin or other P-gp substrates with a NTR.
elagolix	digoxin	1.26	P-gp	May increase plasma concentrations of drugs that are substrates of P-gp.

[1]Both tezcaftor and ivacaftor are P-gp inhibitors *in vitro*, while clinical studies suggest that inhibition of P-gp was likely mainly due to ivacaftor.

Transporter-Based DDIs: NMEs as Inducers

- Only one drug, apalutamide, showed clinical induction of transporters including P-gp, BCRP, and OATP1B1 (Table 6).

Table 6. Transporter-based induction DDIs, NMEs as inducers

Inducer	Substrate	AUCR	Transporter	Label Impact
apalutamide	fexofenadine	0.68	P-gp	Concomitant use with medications that are sensitive substrates of P-gp, BCRP, or OATP1B1 may result in loss of activity of these medications; use caution and evaluate for loss of activity.
	rosuvastatin	0.43	BCRP, OATP1B1	

CONCLUSION

The present analysis evaluated mechanisms involved in PK-based clinical drug interactions triggering label recommendations that involve drugs approved by the FDA in 2018.

For metabolism-based DDIs, it was found that:
- CYP3A plays a major role
- No drugs were sensitive substrates of enzymes
- Dacomitinib was identified as a strong CYP2D6 inhibitor (AUCR of 9.55, dextromethorphan)
- Clinically significant inductions were observed, with apalutamide and ivosidenib being strong inducers of CYP3A/2C19 and CYP3A, respectively

For transporter-based DDIs:
- Elagolix was a sensitive substrate of OATP1B1 (AUCR of 5.58 with single dose rifampin)
- No strong or moderate inhibitors were identified. Fostamatinib showed the highest AUCR of 1.96 in rosuvastatin due to BCRP inhibition
- Apalutamide was a weak-to-moderate inducer of P-gp, BCRP, and OATP1B1 (AUCRs of 0.68 in fexofenadine and 0.43 in rosuvastatin)

Reference:

1. NDA reviews from Drugs@FDA. Website: https://www.accessdata.fda.gov/scripts/cder/daf/ Accessed 2018.