ANALYSIS OF *IN VITRO* TO *IN VIVO* PREDICTIONS OF TRANSPORTER-MEDIATED INHIBITION DRUG INTERACTIONS FOR DRUGS APPROVED BY THE US FOOD AND DRUG ADMINISTRATION BTEWEEN 2013 AND 2016

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ABSTRACT

The present work aimed to systematically review transporter-based *in vitro* and clinical inhibition evaluations of drugs approved by the U.S. Food and Drug Administration (FDA) from 2013 to 2016. *In vitro* inhibition parameters, pharmacokinetics, and clinical drug-drug interaction (DDI) studies available in the New Drug Application (NDA) reviews were analyzed using the University of Washington Drug Interaction Database® (http://www.druginteractioninfo.org/). Following recommendations from the 2012 FDA DDI guidance, *in vitro* to *in vivo* prediction estimates were calculated for the transporters the most often studied.

Overall, 80% of the 103 drugs approved were evaluated *in vitro* as inhibitors of various transporters, with the largest number of New Molecular Entities (NMEs) found to be inhibitors of OATP1B1 (N = 41), followed by P-gp (N = 37), BCRP (N =34), and OATP1B3 (N = 33). Most of these inhibitions however were weak and more than half of the NMEs had prediction values lower than the recommended regulatory cut-offs (0.1 for $[I]_1/IC_{50}$ (or K_i), 10 for $[I]_2/IC_{50}$ (or K_i), 0.1 for total C_{max}/IC_{50}, and 1.25 for R), with no clinical evaluation needed. Among the 22 NMEs inhibiting P-gp with a prediction estimate higher than the cut-off, 16 were evaluated clinically and one was evaluated using PBPK simulations. Ten of them (60%) were found to inhibit P-gp *in vivo*, increasing concentrations of digoxin or simeprevir with AUC ratios of 1.20-1.49 or 2.84, respectively. For BCRP, 20 NMEs had prediction values higher than the cut-off but only 11 of them were further evaluated clinically, with 9 NMEs (82%) showing clinical inhibition (34-159% increase in the exposure of the BCRP substrates rosuvastatin, sofosbuvir, sulfasalazine, or tenofovir). With regards to OATP1B1/3, 13 NMEs had prediction values higher than the cut-off. Almost all of them (N = 12) had a clinical study with an OATP1B1/3 substrate, mainly a statin, with 10 NMEs significantly increasing the substrate exposure up to 3-fold. For drugs with prediction values higher than the cut-offs but not evaluated clinically (N = 5, 9, and 1 for P-gp, BCRP, and OATP1B1/3, respectively), a clinical evaluation was either recommended or requested in 1/3 of the cases as a post marketing study. Interestingly, nine drugs were evaluated clinically for their potential to inhibit P-gp or OATP1B1/3, although they had prediction values lower than the cut-off. Two of them showed a significant clinical inhibition that triggered label recommendations, namely flibanserin for P-gp and eluxadoline for OATP1B1. On the other hand, among the 11 drugs with estimates higher than the cut-offs but no effect on marker substrate exposure, eight drugs had high (> 98%) plasma protein binding, suggesting that the use of unbound inhibition parameters and free plasma concentrations in the calculation methods recommended in the most recent FDA DDI guidance (2017) will improve predictions for highly bound drugs.

OBJECTIVES

- To review transporter-mediated *in vitro* and clinical inhibition data available in the most recent NDAs (2013-2016).
- Using the most studied transporters as examples, to evaluate regulatory cut-offs for *in vitro* to *in vivo* predictions.

RESULTS

In Vitro Inhibition

- Most NMEs and metabolites were extensively evaluated for their potential to inhibit drug transporters (ranging from 73% in 2014 to 93% in 2016). A total of 21 transporters were evaluated.
- The largest number of NMEs were found to inhibit OATP1B1 (N = 41), followed by P-gp (N = 37), BCRP (N = 34), and OATP1B3 (N = 33) (Figure 1).

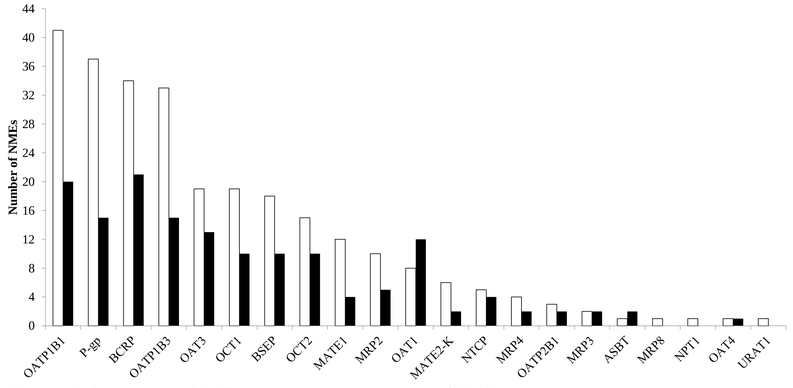

Figure 1. Number of NMEs inhibiting transporters (NMEs, open bars; metabolites, closed bar)

OATP1B1/1B3

- Thirteen drugs had prediction estimates greater than the FDA cut-off value (total $C_{max}/IC_{50} \geq 0.1$) (Table 1).
- Twelve of these precipitants had a clinical study with an OATP1B1/1B3 substrate (statin), with 10 (83%) NMEs significantly increasing statin exposure up to 3-fold and eight of them triggering label recommendations (reduce statin dose or monitor patients for adverse reactions) (Table 1).
- One drug (eluxadoline), with weak inhibition of OATP1B1 and total $C_{max}/IC_{50} < 0.1$, showed clinically meaningful inhibition (AUC ratio = 1.41, rosuvastatin).

Table 1. Drugs inhibiting OATP1B1/1B3 with prediction estimates ≥ cut-off value

Precipitant	OATP	IC_{50} (µM)	C_{max}/IC_{50}	% Bound	AUC Ratio	Reference
Clinical DDIs with AUC ratios ≥ 1.25						
Daclatasvir	1B1	2.3	1.02	~ 99	1.47 (rsv) [a]	DAKLINZA
	1B3	5.7	0.41			
Dasabuvir	1B1	0.9	2.32	99.5	2.59 (rsv) [a], 1.82 (prv) [a]	VIEKIRA PAK
	1B3	6.6	0.32			
Elbasvir	1B3	0.1	1.37	> 99.9	1.95 (atv) [a]	ZEPATIER
Grazoprevir	1B1	0.7	0.31	> 98.8	3.00 (atv) [a], 1.33 (prv), 1.11 (ptv)	ZEPATIER
	1B3	1.1	0.20			
Isavuconazonium sulfate	1B1	11.2	1.53	> 99	1.40 (atv) [a]	CRESEMBA
Obeticholic acid	1B1	2.57	0.10	> 99	1.22-1.30 (rsv)	OCALIVA
	1B3	2.15	0.12			
Paritaprevir	1B1	0.031	61.9	98.6	2.59 (rsv) [a], 1.82 (prv) [a]	VIEKIRA PAK
	1B3	0.017	113			
Sacubitril	1B1	1.9	3.11	~ 97	1.30 (atv)	ENTRESTO
Simeprevir	1B1	0.26	55.9		2.81 (rsv) [a], 2.19 (atv) [a], 1.71 (smv) [a]	OLYSIO
Velpatasvir	1B1	1.5	0.20	> 99.5	2.69 (rsv) [a], 1.35 (prv)	EPCLUSA
	1B3	0.26	1.13			EPCLUSA
Clinical DDIs with AUC ratios < 1.25						
Idelalisib	1B1	10	0.46	> 84	1.11 (rsv)	ZYDELIG
	1B3	7	0.66			
Lesinurad	1B1	9.3	1.83	> 98	1.01 (atv)	ZURAMPIC
	1B3	43.1	0.40			
Clinical relevance not evaluated						
Lenvatinib	1B1	7.29	0.21	98-99	N/T	LENVIMA
	1B3	3.8	1.55			

[a] label recommendations were triggered; atr, atorvastatin; ptv, pitavastatin; prv, pravastatin; rsv, rosuvastatin; smv, simvastatin; N/T: not tested; R values are not presented because no drugs had R ≥ 1.25

Table 2. Drugs inhibiting P-gp (substrate: digoxin) with prediction estimates ≥ cut-off values

Precipitant	IC_{50} (µM)	$[I]_1/IC_{50}$	$[I]_2/IC_{50}$	% Bound	AUC Ratio	Reference
Clinical DDIs with AUC ratios ≥ 1.25 or with label impact						
Canagliflozin	19.3	0.54	137	98.3-99.2	1.20 [a]	INVOKANA
Daclatasvir	4.4	0.53	74	~ 99	1.27 [a]	DAKLINZA
Eliglustat	22	0.02	37.8	62	1.49 [a]	CERDELGA
Ibrutinib	4.9	0.06	1038	97.3	N/P [a,b]	IMBRUVICA
Isavuconazonium sulfate	25.7	0.67	71	> 99	1.25 [a]	CRESEMBA
Ledipasvir	~1	0.36	405	> 99.8	2.84 [a,c]	HARVONI
Rolapitant	7.36	0.23	196	99.8	1.27 [a]	VARUBI
Simpeprevir	85.9	0.17	12.4	> 99.9	1.39 [a]	OLYSIO
Suvorexant	18.7	0.05	18.9	> 99	1.27 ($AUC_{0\text{-}last}$) [a]	BELSOMRA
Velpatasvir	20.6	0.01	22	> 99.5	1.34 [a]	EPCLUSA
Clinical DDIs with AUC ratios < 1.25						
Afatinib	3.4 (K_i)	0.02	97	57.2-88.4	N/P [d]	GILOTRIF
Dasabuvir	16.7	0.12	121	99.5	1.16	VIEKIRA PAK
Elbasvir	0.32	0.43	709	> 99.9	1.11	ZEPATIER
Idelalisib	8	0.58	181	> 84	1.00	ZYDELIG
Netupitant	5 [e]	0.25	415	> 99.5	1.04	AKYNZEO
Paritaprevir	38.1	0.05	21	98.6	1.16	VIEKIRA PAK
Vorapaxar	1.2	0.13	14.1	> 99.8	1.05	ZONTIVITY
Clinical relevance not evaluated						
Alectinib*	1.1	1.20	4521	> 99	N/T [f]	ALECENSA
Rucaparib	283	0.02	37	70	PMR	RUBRACA
Uridine triacetate	344	< 0.1	108	N/P	N/T	XURIDEN
Venetoclax	0.79	3.06	2332	> 99.9	PMR [a]	VENCLEXTA
Vortioxetine	4.4	0.01	24	98	N/T	BRINTELLEX

[a] label recommendations were triggered; [b] absorption-based PBPK simulations were used; [c] simeprevir was used as the substrate; [d] analyses were conducted from other clinical studies; [e] The IC_{50} value was assumed based on the observation that the efflux ratio was reduced from 29 to 4.7 at 5 µM; [f] clinical trials recommended; $[I]_1$ represents the mean steady state total C_{max} following administration of the highest proposed clinical dose; $[I]_2$ = dose of inhibitor (in mol)/250 mL; N/P, no provided; N/T, not tested; PMR, post-marketing requirement

P-gp

- Twenty-two drugs had prediction estimates greater than the FDA cut-offs ($[I]_1/IC_{50} \geq 0.1$ and/or $[I]_2/IC_{50} \geq 10$) (Table 2).
- Sixteen precipitants were evaluated clinically and one was assessed with PBPK simulations. Among them, 10 NMEs (60%) were found to inhibit P-gp *in vivo*, increasing the exposure of digoxin or simeprevir 20-49% or 184%, respectively, and triggering label recommendations (reduce digoxin dose, monitor patients for adverse reactions, or not recommend for co-administration) (Table 2).
- One drug (flibanserin), with weak inhibition and lower prediction estimate, showed clinically meaningful inhibition (AUC ratio = 1.96, digoxin).
- Two NMEs (alogliptin and eslicarbazapine acetate) were only evaluated clinically without *in vitro* inhibition assessment and showed no clinically meaningful inhibition.

BCRP

- Twenty drugs had prediction estimates greater than the FDA cut-offs ($[I]_1/IC_{50} \geq 0.1$ and/or $[I]_2/IC_{50} \geq 10$) (Table 3).
- Only 11 of them were evaluated clinically, with nine NMEs (82%) showing clinical inhibition (34-159% increase in the exposure of BCRP substrates) and triggering label recommendations (reduce victim drug dose or monitor for adverse reactions) (Table 3).

Table 3. Drugs inhibiting BCRP with prediction estimates ≥ cut-off values

Precipitant	IC_{50} (µM)	$[I]_1/IC_{50}$	$[I]_2/IC_{50}$	% Bound	AUC Ratio	Reference
Clinical DDIs with AUC ratios ≥ 1.25						
Daclatasvir	10.9	0.21	30	~ 99	1.47 (rsv) [a]	DAKLINZA
Dasabuvir	15.6	0.13	130	99.5	2.59 (rsv) [a]	VIEKIRA PAK
Elbasvir	0.15	0.91	1512	> 99.9	1.34 (AUC_{24h})(tfv) [a]	ZEPATIER
Grazoprevir	12.5	0.02	42	> 98.8	1.59 (rsv) [a]	ZEPATIER
Osimertinib	2	0.04	320	N/P	1.35 (rsv) [a]	TAGRISSO
Paritaprevir	0.59	3.25	1328	98.6	2.59 (rsv) [a]	VIEKIRA PAK
Rolapitant	0.172	10	8366	99.8	2.18 (sfs) [a]	VARUBI
Tedizolid (phosphate)	51.1	0.16	32	70-90	1.70 (rsv) [a]	SIVEXTRO
Velpatasvir	0.3	0.98	1510	> 99.5	2.38 (sfr) [b]	EPCLUSA
Clinical DDIs with AUC ratios < 1.25						
Brexpiprazole*	1.16	0.40	32	> 99	1.12 (rsv)	REXULTI
Isavuconazonium sulfate	92	0.02	20	> 99	No effect (mtx)	CRESEMBA
Clinical relevance not evaluated						
Afatinib	0.75	0.10	439	57.2-88.4	N/T	GILOTRIF
Alectinib*	0.1	13	49730	> 99	N/T [c]	ALECENSA
Cobimetinib	3.3	0.16	137	95	N/T	COTELLIC
Netupitant*	6	0.25	346	> 99.5	N/T [c]	AKYNZEO
Rucaparib	55	0.11	189	70	N/T	RUBRACA
Sonidegib	1.5	0.98	783	> 97	N/T	ODOMZO
Suvorexant	10-15	0.12	10.6	> 99	N/T	BELSOMRA
Trametinib	1.1	0.04	10.5	96-97.4	N/T	MEKINIST
Venetoclax	0.13	18.6	14172	> 99.9	N/T	VENCLEXTA

[a] label recommendations were triggered; [b] combo drug; [c] clinical trials recommended; ; $[I]_1$ represents the mean steady state total C_{max} following administration of the highest proposed clinical dose; $[I]_2$ = dose of inhibitor (in mol)/250 mL; N/P, no provided; N/T, not tested; mtx, methotrexate; rsv, rosuvastatin; sfr, sofosbuvir; sfs, sulfasalazine; tfr, tenofovir

CONCLUSIONS

- A significant number of recently approved NMEs were found to inhibit OATP1B1/1B3, P-gp, and BCRP *in vitro*.
- Among drugs with prediction estimates higher than the FDA cut-off values for clinical evaluation:
  - Approximately 75% were evaluated clinically or using PBPK simulations, with 70-80% showing clinically meaningful inhibition with label recommendations
  - For the 25% not evaluated, 1/3 had a PMR or recommendation to conduct a clinical trial
- Among drugs with lower prediction estimates, seven drugs were still evaluated clinically and two of them showed clinical inhibition with dose recommendations triggered, indicating a risk of "*false negative*" using prediction methods recommended in the 2012 FDA DDI guidance.
- Considering that most of the precipitants had high plasma protein binding (Tables 1-3), the use of unbound inhibition parameters and free plasma concentrations in the calculation methods, as recommended by the most recent DDI guidance (FDA, 2017), is expected to improve predictions.