Critical Review of the Literature 2017-2018

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Outline

1- DDI Publications: What is new in 2017-2018?

Publications: updates and trends

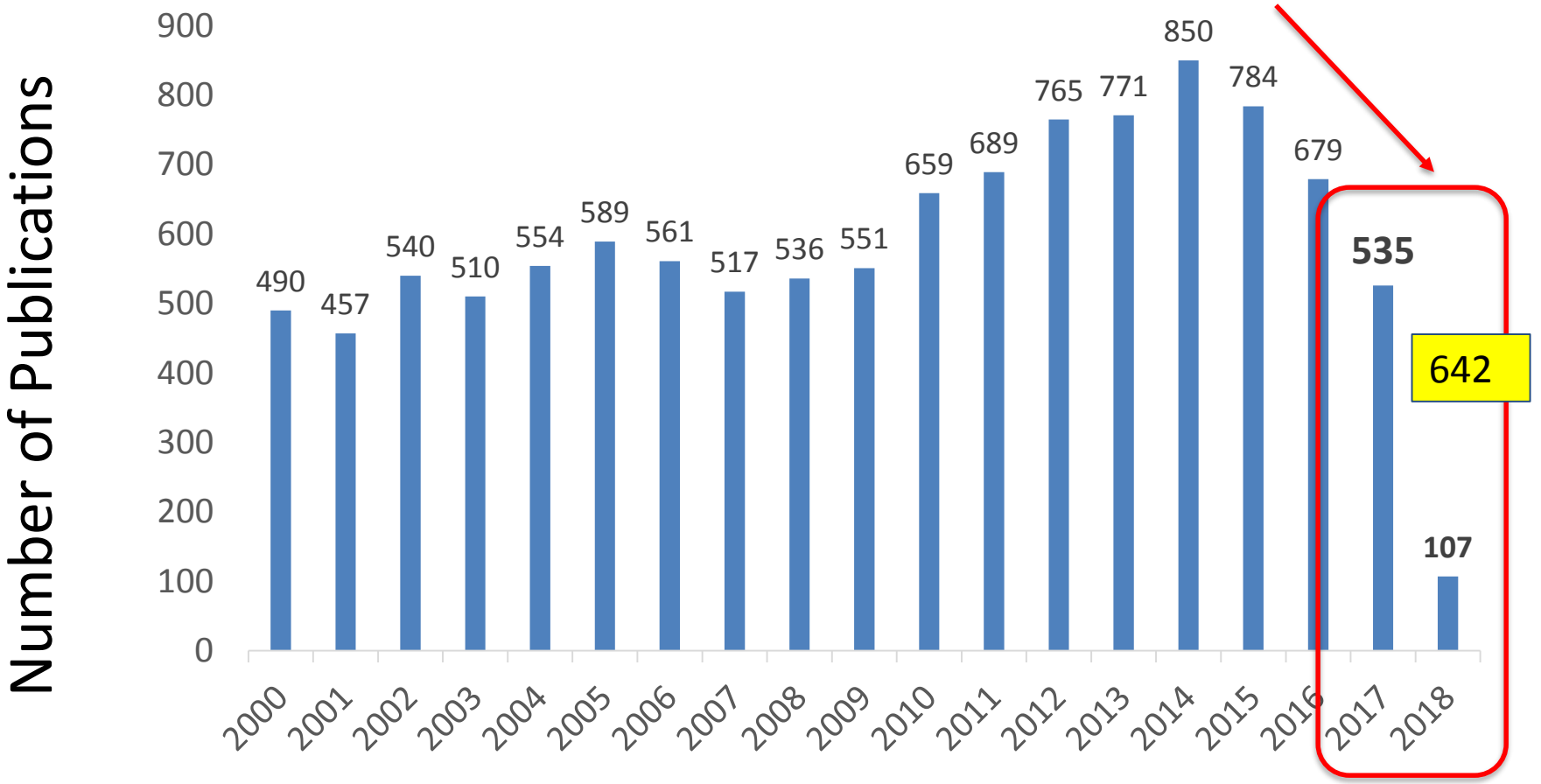
Most pronounced clinical DDIs

Transporter-based clinical DDIs

2- 2017-2018 Highlight: Example of *in vivo* gene-drug-drug-interactions (GDDIs)

"Notable Drug-Drug Interaction Between Etizolam and Itraconazole in Poor Metabolizers of Cytochrome P450 2C19."

Number of Publications Entered in UW DIDB Platform



- Decrease in number of publications in past few years
- However, each publication now includes more studies

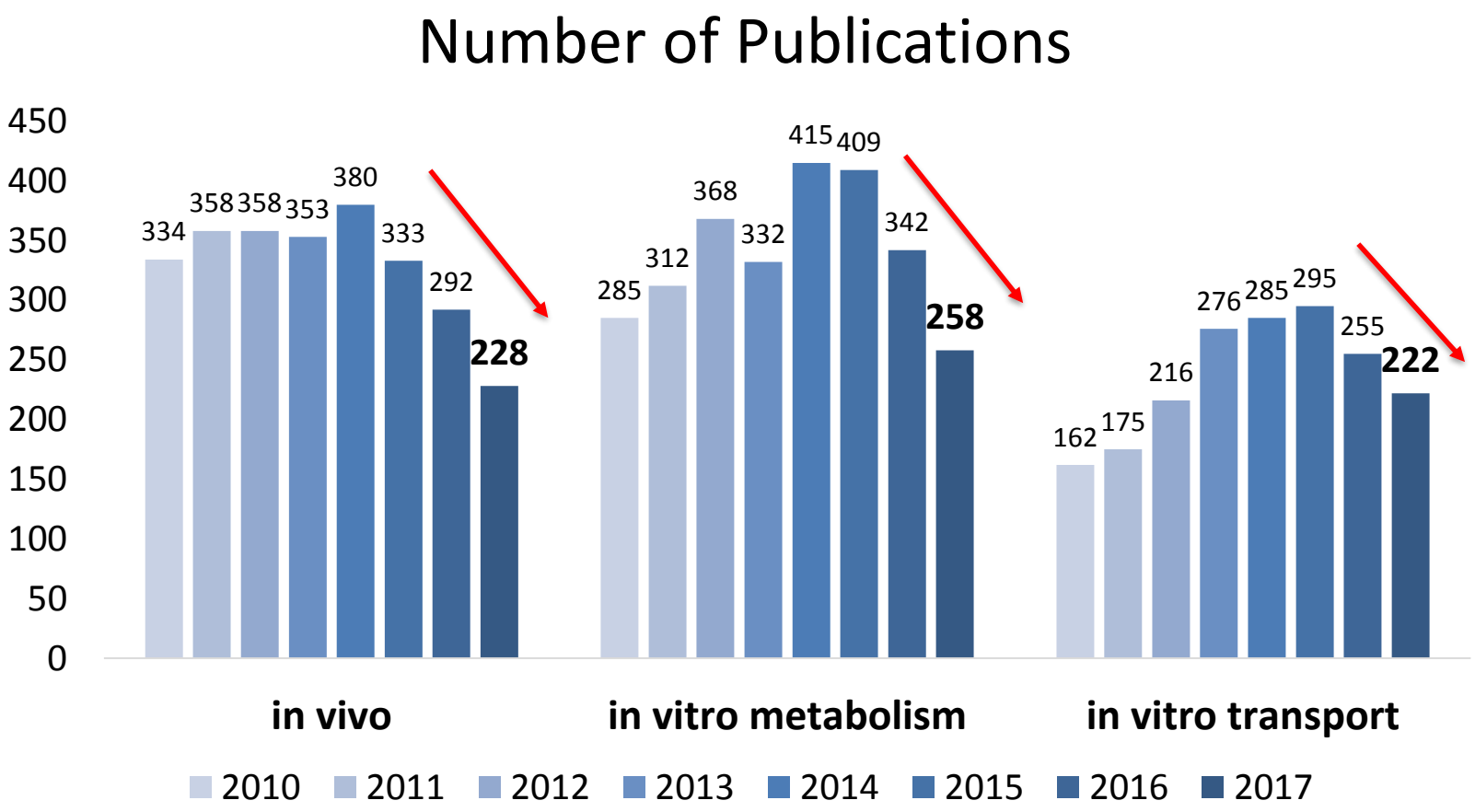
Top 10 Journals (2017)

contribute ~43% of the published articles

Journal	Number of Articles	Overall Percentage	Primary focus
Drug Metab Dispos	48	9.1	*in vitro*
Xenobiotica	36	6.8	*in vitro*
J Pharm Sci	28	5.3	*in vitro*
Br J Clin Pharmacol	23	4.4	*in vivo*
J Clin Pharmacol	20	3.8	*in vivo*
Clin Pharmacol Drug Dev	19	3.6	*in vivo*
Antimicrob Agents Chemother	15	2.8	*in vivo*
Eur J Drug Metab Pharmacokinet	14	2.6	*in vitro* / *in vivo*
Eur J Clin Pharmacol	12	2.3	*in vivo*
Biopharm Drug Dispos	11	2.0	*in vitro* / *in vivo*

- Changes in the journals' scientific coverage in recent years
- DDI publications seem to be distributed more broadly

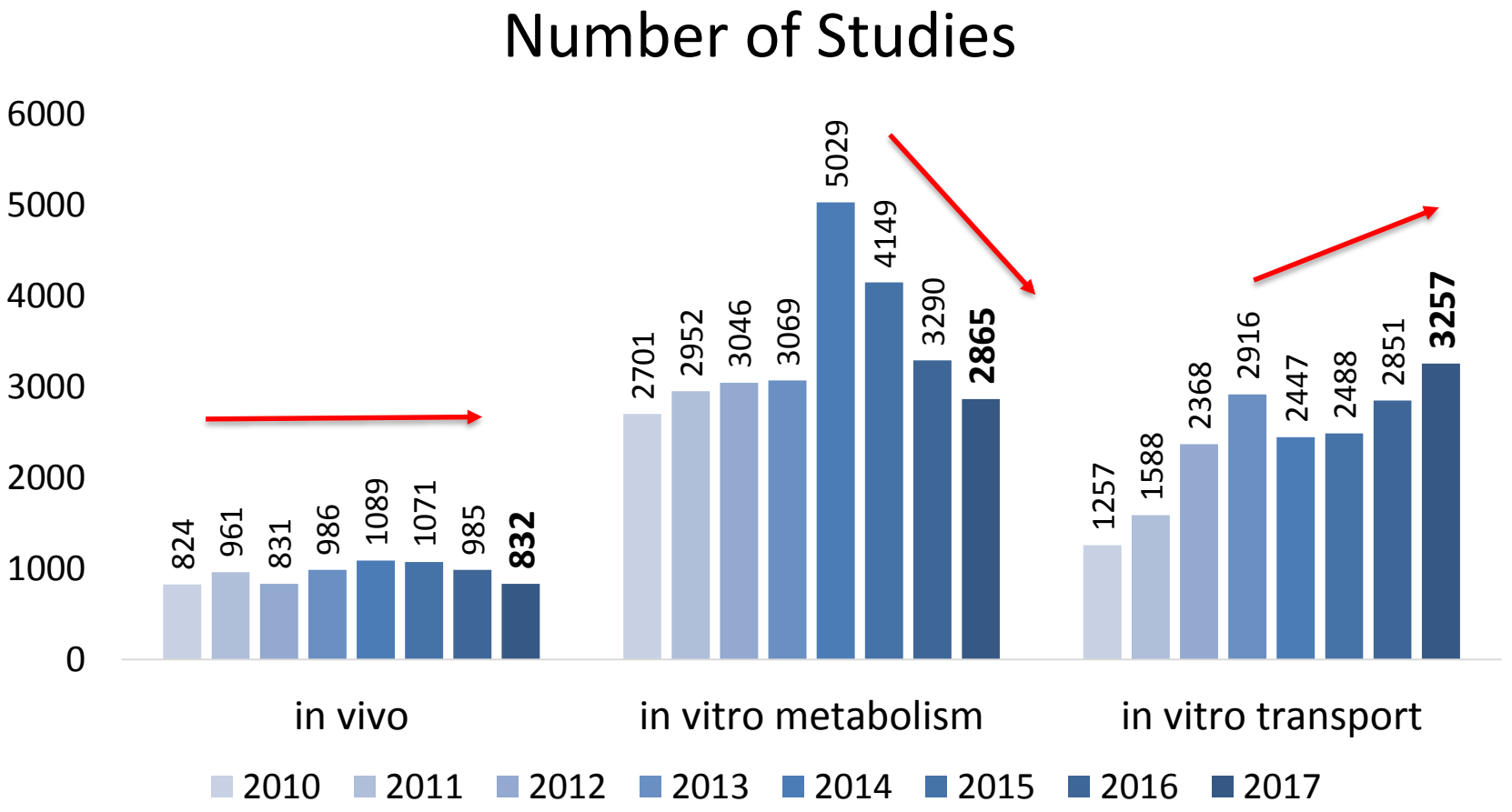
Types of Articles* (2010-2017)



Recent decrease in number of publications is observed for all types of citations

*articles can contain both *in vitro* and *in vivo* studies

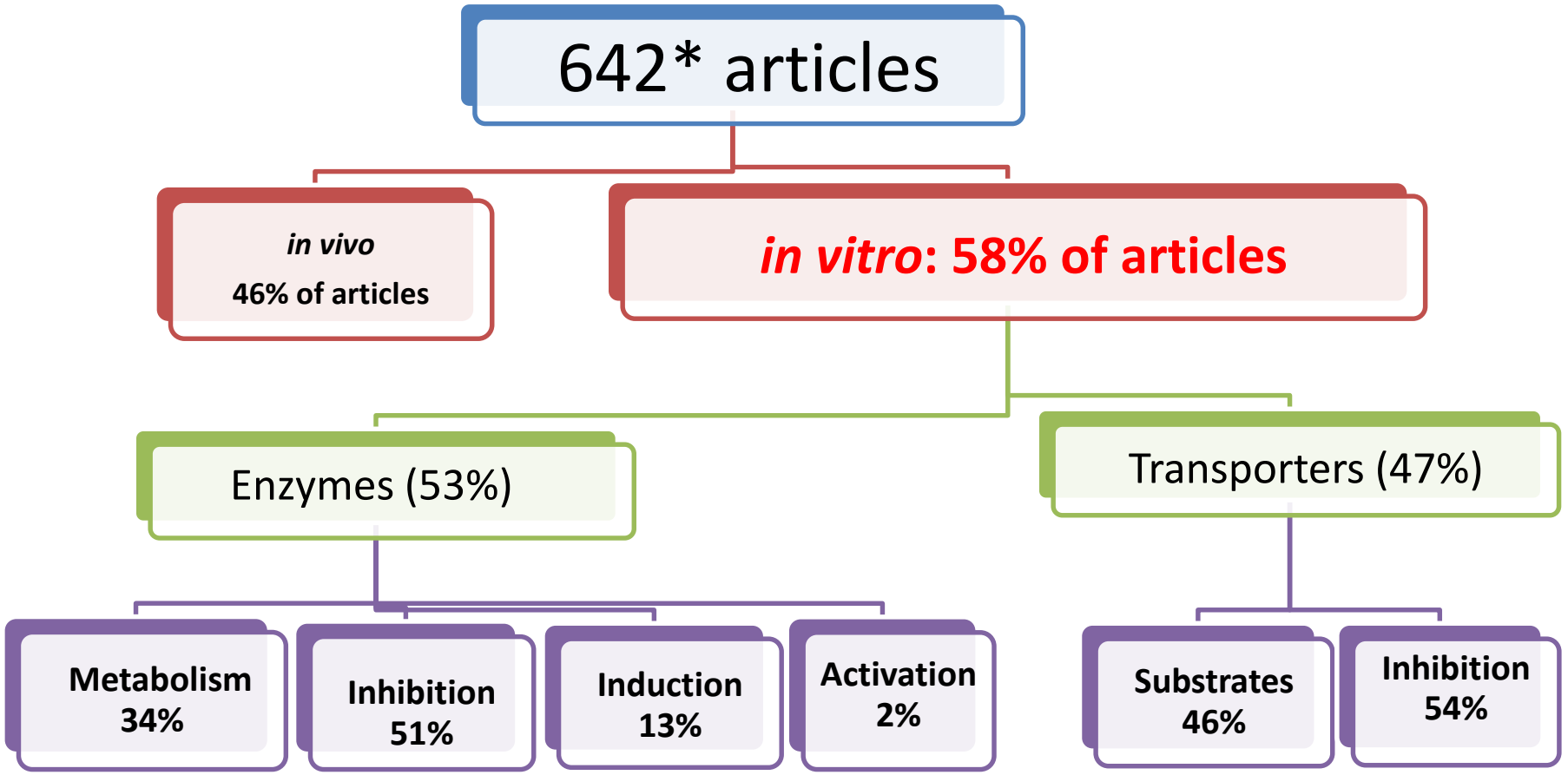
Types of Articles* (2010-2017)



Overall amount of information (i.e. number of studies) relatively stable

*articles can contain both *in vitro* and *in vivo* studies

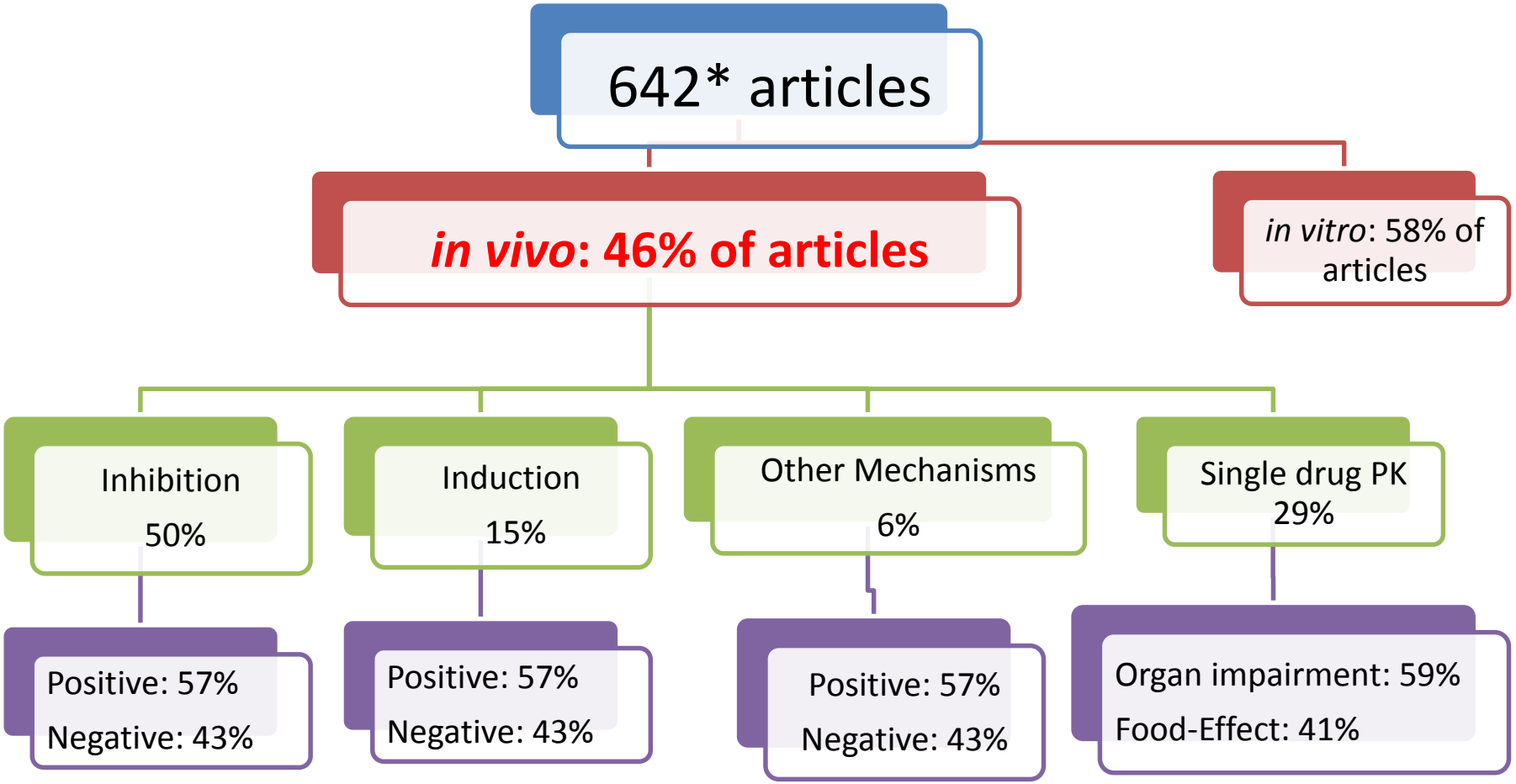
Articles 2017-2018



- There are 25% more *in vitro* than *in vivo* articles
- Among *in vitro* papers, transporter-based DDIs are catching up with metabolism-based DDIs

*23 articles contain both *in vivo* and *in vitro* information and are included in each category

Articles 2017-2018



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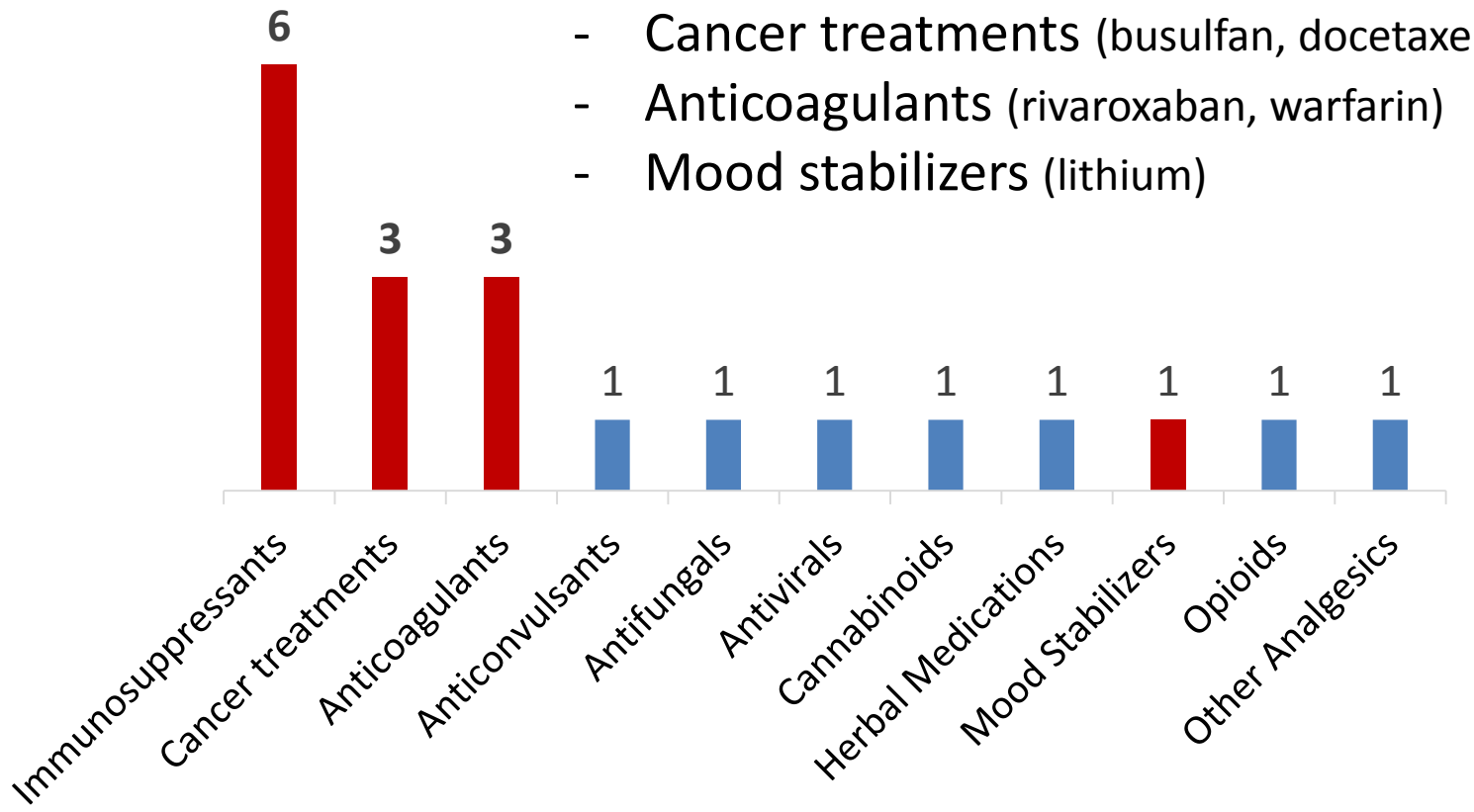
Case Reports of Toxicity (N = 20)

victims involved

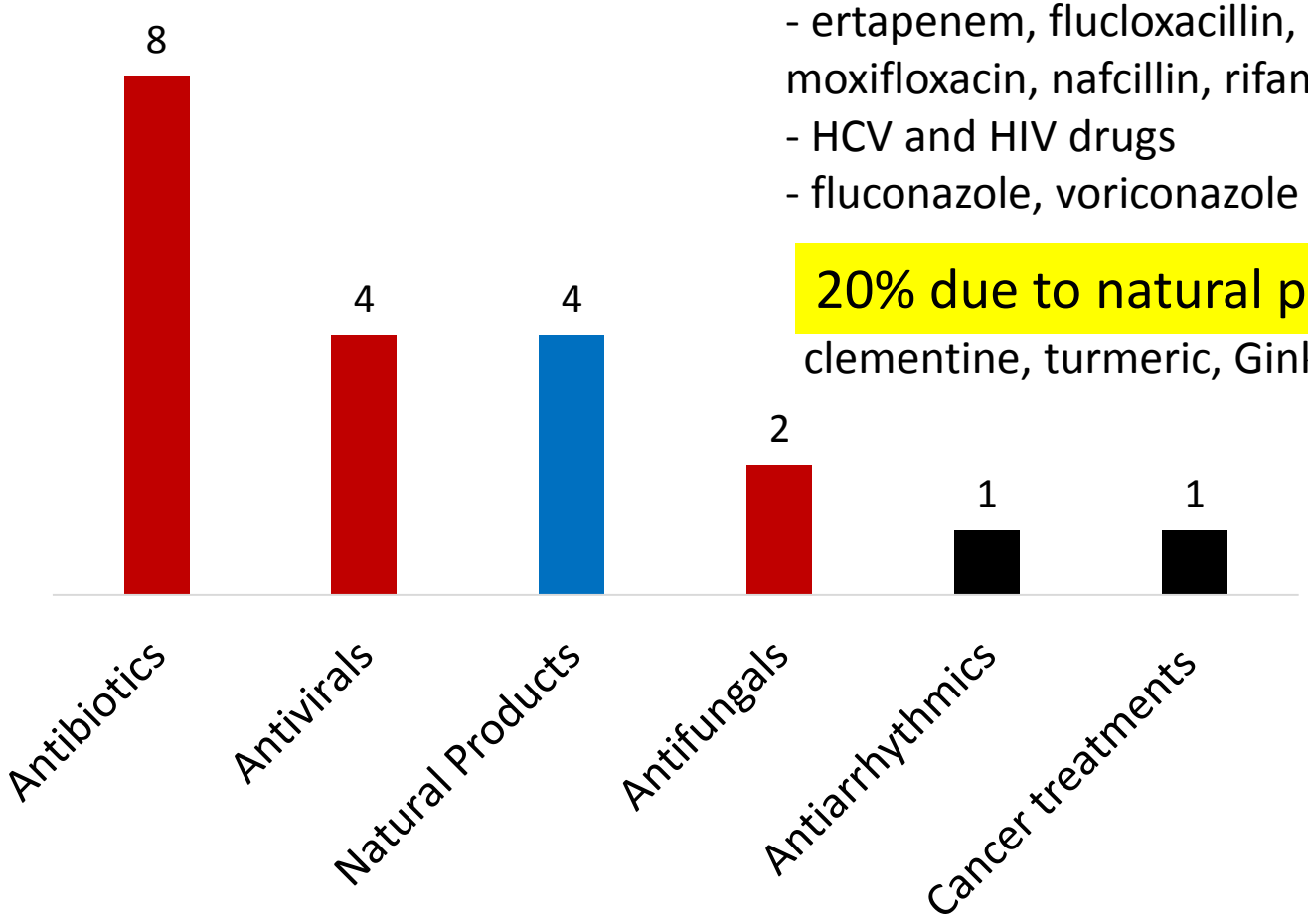
65% of the victims are NTI drugs

- Immunosuppressant (tacrolimus, everolimus)
- Cancer treatments (busulfan, docetaxel, vinblastine)
- Anticoagulants (rivaroxaban, warfarin)
- Mood stabilizers (lithium)



Case Reports of Toxicity (N = 20)

perpetrators involved



70% due to anti-infective drugs

- ertapenem, flucloxacillin, meropenem, moxifloxacin, nafcillin, rifampin
- HCV and HIV drugs
- fluconazole, voriconazole

20% due to natural products

clementine, turmeric, Ginkgo biloba, garlic

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Most Pronounced Clinical Inhibitions (Top 10)

Victim	Inhibitor	Enzymes / Transporters	Victim AUC ratio	Reference
trifluridine	tipiracil	thymidine phosphorylase	35.2	Cleary, 2017
dextromethorphan	GSK1034702	CYP2D6	21.8	Hobbs, 2017
ivacaftor	ritonavir	CYP3A	19.7	Liddy, 2017
rosuvastatin	**faldaprevir**	**OATP1B1/1B3**	**14.7**	Huang, 2017
venetoclax	posaconazole	CYP3A	9.7	Agarwal, 2017
atorvastatin	**faldaprevir**	**OATP1B1/1B3**	**9.4**	Huang, 2017
atorvastatin	**rifampin SD**	**OATP1B1/1B3**	**8.6**	Prueksaritanont, 2017
venetoclax	ketoconazole	CYP3A, (P-gp, BCRP)	7.9	Agarwal, 2017
pibrentasvir	**glecaprevir**	**P-gp, BCRP**	**7.5**	Lin, 2018
simeprevir	**rifampin SD**	**OATP1B1/1B3**	**7.4**	Yoshikado, 2017
midazolam	itraconazole	CYP3A	7.1	Prueksaritanont, 2017

- Transporters (OATP1B1/1B3 inhibition) contribute as much as metabolic enzymes
- Most perpetrators are anti-infective drugs (consistent with role of antibiotics in previous slide)
- All victims are marker or sensitive substrates

Most Pronounced Clinical Inductions (Top 10)

Victim	Inducer	Enzymes / Transporters possibly involved	Victim AUC ratio	Reference
isavuconazole	rifampin	**CYP3A**	0.12	Townsend, 2017
doravirine	rifampin	**CYP3A**	0.13	Yee, 2017
odanacatib	rifampin	**CYP3A**, P-gp	0.16	Stoch, 2017
omeprazole	rifampin	**CYP3A**, CYP2C19	0.17	Park, 2017
amenamevir	rifampin	**CYP3A**	0.17	Kusawake, 2017
apatinib	rifampin	**CYP3A**	0.19	Liu, 2018
istradefylline	rifampin	**CYP3A**, CYP2B6, CYP2C8, CYP2C9	0.26	Mukai, 2018
alectinib	rifampin	**CYP3A**	0.26	Morcos, 2017
ixazomib	rifampin	CYP1A2, CYP2B6, other enzymes, P-gp	0.27	Gupta, 2018
sonidegib	rifampin	**CYP3A**	0.29	Einolf, 2017

- CYP3A induction is the predominant mechanism
- All most pronounced inductions are due to rifampin
- Victims: mostly cancer treatments and anti-infective drugs

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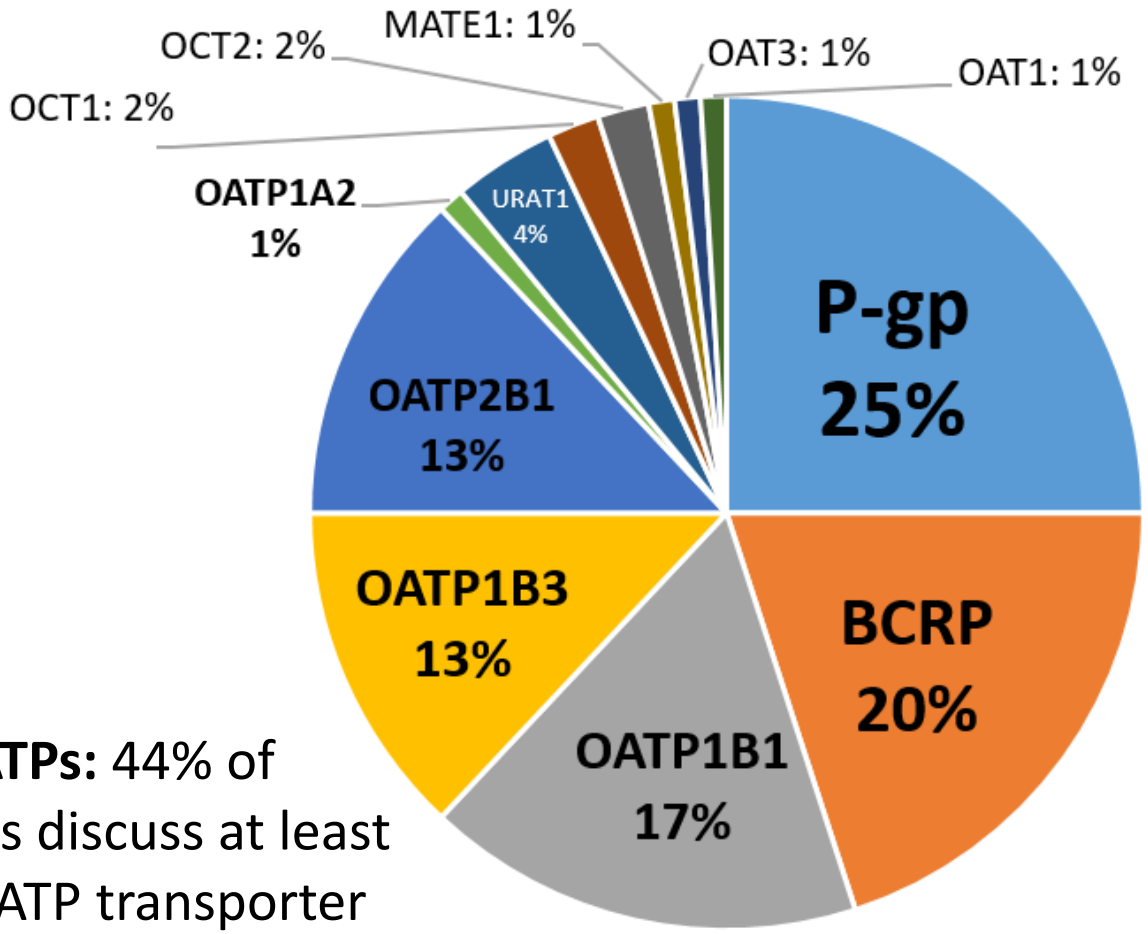
In vivo Articles Discussing Role of Transporters in DDIs



P-gp and BCRP: significant contributors to clinical DDIs

All OATPs: 44% of articles discuss at least one OATP transporter

P-gp Related Inhibition

Victim	Perpetrator	Perpetrator Dose (oral)	Victim AUC ratio	Reference
Markers				
dabigatran E (μ dose)	itraconazole	200 mg QD [5 days]	6.9	Prueksaritanont, 2017
dabigatran E (μ dose)	clarithromycin	500 mg BID [5 days]	4.0	Prueksaritanont, 2017
dabigatran E	cobicistat	150 mg QD [22 days]	2.4	Kumar, 2017
dabigatran E	rifampin	600 mg SD	2.3	Prueksaritanont, 2017
dabigatran E	clarithromycin	500 mg BID [5 days]	2.1	Gouin-Thibault, 2017
digoxin	rolapitant	180 mg SD	1.3	Wang, 2018
digoxin	mirabegron	100 mg QD [14 days]	1.3	Groen-Wijnberg, 2017
fexofenadine	piperine	20 mg QD [10 days]	1.7	Bedada, 2017
fexofenadine	diosmin	150 mg QD [10 days]	1.7	Bedada, 2017
Co-Meds				
simeprevir*,¥	ledipasvir	90 mg QD [14 days]	3.0	Bourgeois, 2017
rivaroxaban	clarithromycin	500 mg BID [5 days]	2.1	Gouin-Thibault, 2017
rosuvastatin*	itraconazole	200 mg QD [5 days]	1.8	Prueksaritanont, 2017
glecaprevir*,¥	pibrentasvir	160 mg QD [7 days]	1.8	Lin, 2018
ledipasvir¥	simeprevir	150 mg QD [14 days]	1.7	Bourgeois, 2017
atorvastatin	isavuconazole	200 mg TID [8 days]	1.3	Yamazaki, 2017
peficitinib	verapamil	80 mg TID [10 days]	1.3	Zhu, 2017

*BCRP also involved; ¥OATPs also involved

P-gp related inhibition rarely over 2-fold except with dabigatran etexilate

Hepatic OATP-Related Inhibition

Victim	Perpetrator	Perpetrator dose (oral)	Victim AUC ratio	Transporter(s) involved	Reference
Markers					
rosuvastatin	faldaprevir	240 mg QD [6 days]	14.7	OATP1B, P-gp	Huang, 2017
atorvastatin	faldaprevir	240 mg QD [6 days]	9.4	OATP1B, P-gp	Huang, 2017
atorvastatin	rifampin	600 mg SD	8.6	OATP1B, BCRP	Prueksaritanont, 2017
rosuvastatin	rifampin	600 mg SD	4.6	OATP1B, BCRP	Prueksaritanont, 2017
pitavastatin	rifampin	600 mg SD	4.2	OATP1B	Prueksaritanont, 2017
atorvastatin*	clarithromycin	500 mg BID [5 days]	3.4	OATP1B	Prueksaritanont, 2017
rosuvastatin	rifampin	600 mg SD (IV)	3.4	OATP1B, BCRP	Wu, 2017
rosuvastatin	rifampin	600 mg SD (IV)	3.2	OATP1B, BCRP	Wu, 2017
repaglinide ←	rifampin	600 mg SD	1.9	OATP1B	Yoshikado, 2017
rosuvastatin	clarithromycin	500 mg BID [5 days]	1.6	OATP1B	Prueksaritanont, 2017
rosuvastatin	peficitinib	150 mg [9 days]	1.3	OATP1B	Zhu, 2017
Endogenous Compounds					
coproporphyrin I	rifampin	600 mg SD	4.0	OATP1B	Shen, 2017
coproporphyrin III	rifampin	600 mg SD	3.3	OATP1B	Shen, 2017
tetradecanedioate	rifampin	600 mg SD	3.2	OATP1B	Shen, 2017
hexadecanedioate	rifampin	600 mg SD	2.4	OATP1B	Shen, 2017

*CYP3A also involved

Recent publications evaluate the use of endogenous compounds (coproporphyrin I and III) as potential specific OATP1B markers to study OATP1B-related clinical inhibition

Hepatic OATP-Related Inhibition

Victim	Perpetrator	Perpetrator dose (oral)	Victim AUC ratio	Transporter(s) involved	Reference
Co-Meds					
simeprevir	rifampin	600 mg SD	7.2	OATP1B	Yoshikado, 2017
letermovir	cyclosporine	200 mg SD	3.4	OATP1B P-gp, BCRP	Kropeit, 2018
bosentan	rifampin	600 mg SD	3.2	OATP1B	Yoshikado, 2017
selexipag	gemfibrozil	600 mg BID [9 days]	2.0	OATP1B	Bruderer, 2017
clarithromycin	rifampin	600 mg SD	1.9	OATP1B	Yoshikado, 2017
glecaprevir	pibrentasvir	160 mg QD [7 days]	1.8	OATP1B P-gp, BCRP	Lin, 2018

Inhibition of hepatic OATPs can lead to significant increases in substrate exposures

Intestinal OATP2B1-Related Inhibition

Victim	Perpetrator	Perpetrator Dose (oral)	Victim AUC ratio	Reference
glibenclamide	grapefruit juice	200 mL TID [3 days]	0.5	Kashihara, 2017
rosuvastatin	ronacaleret	400 mg QD [10 days]	0.5	Johnson, 2017
celiprolol	grapefruit juice	200 mL TID [3 days]	0.6	Kashihara, 2017
rosuvastatin	grapefruit juice	200 mL TID [3 days]	0.7	Kashihara, 2017
sulfasalazine	grapefruit juice	200 mL TID [3 days]	0.7	Kashihara, 2017
sumatriptan	grapefruit juice	200 mL TID [3 days]	0.7	Kashihara, 2017
rosuvastatin	epigallocatechin gallate	300 mg SD	0.8	Kim, 2017

Ronacaleret: investigational drug candidate for treatment of osteoporosis (now terminated)
Glibenclamide, rosuvastatin and sulfasalazine are dual substrates for OATP2B1 and BCRP

Inhibitors of intestinal OATP2B1 are mostly natural products

DDI Publications 2017-2018: Conclusions

- Literature
  Overall, same amount of information available despite a decrease in number in published articles
  More *in vitro* transport data becoming available
- Most pronounced clinical interactions
  Inhibition: significant contribution of hepatic OATPs
  Induction: rifampin used as a multi-CYP inducer
- Transporter-based DDIs
  Investigation of new potential endogenous markers for OAPT1B-based DDIs

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Example of Gene-Drug-Drug-Interactions (GDDIs)

Case Study

Notable Drug-Drug Interaction Between Etizolam and Itraconazole in Poor Metabolizers of Cytochrome P450 2C19.

Yamamoto T, Furihata K, Hisaka A, Moritoyo T, Ogoe K, Kusayama S, Motohashi K, Mori A, Iwatsubo T, Suzuki H.

J Clin Pharmacol. 2017 Nov;57(11):1491-1499.

DDI Between Etizolam and Itraconazole in CYP2C19 Poor Metabolizers

Victim: etizolam

- Thienodiazepine
- Anxiety disorder with depression, panic disorder and insomnia
- Relatively safe - low abuse potential
- Marketed in Italy, South Korea and Japan
- One of the most prescribed benzodiazepines in Japan
- Metabolism*: CYP2C19 and CYP3A

Perpetrator: itraconazole

- Antifungal
- Strong CYP3A inhibitor

CYP2C19 polymorphisms

- Japanese: ~20% are poor Metabolizers

*Ref: *In vitro*: Niwa, 2005
In vivo: Araki, 2004; Suzuki, 2004; Kondo, 2005; Fukasama, 2005

DDI Between Etizolam and Itraconazole in CYP2C19 Poor Metabolizers

in vitro experiments: estimation of etizolam f_{mCYP3A}

Experiments

- Human liver microsomes prepared from CYP2C19 PM donors
- Etizolam: 0.2 or 1.0 µM
- Itraconazole: 0, 0.0015, 0.56, 1.4, 3.5, or 8.7 µM

Results: fraction metabolized by CYP3A

- f_{mCYP3A} etizolam: 0.60 ± 0.06
- $K_{i,\ itraconazole}$: 0.73 ± 0.28 µM

Based on the estimated f_m value, the magnitude of increase in AUC_∞ was estimated 2.5-fold *in vivo*.

J Clin Pharmacol. 2017 Nov;57(11):1491-1499.

DDI Between Etizolam and Itraconazole in CYP2C19 Poor Metabolizers

in vivo study

Subjects and study design:

16 healthy male Japanese volunteers: CYP2C19 EMs (N = 8)
CYP2C19 PMs (N = 8)

Fixed-sequence

Etizolam administration

0.25 mg single dose (9:00 am)
alone on Day 1 and with itraconazole on Day 5

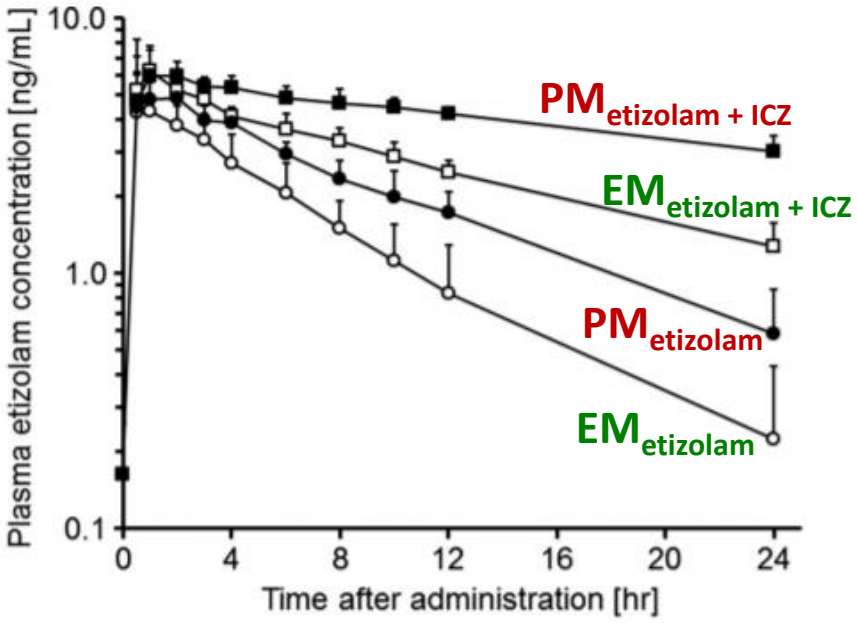
Itraconazole administration

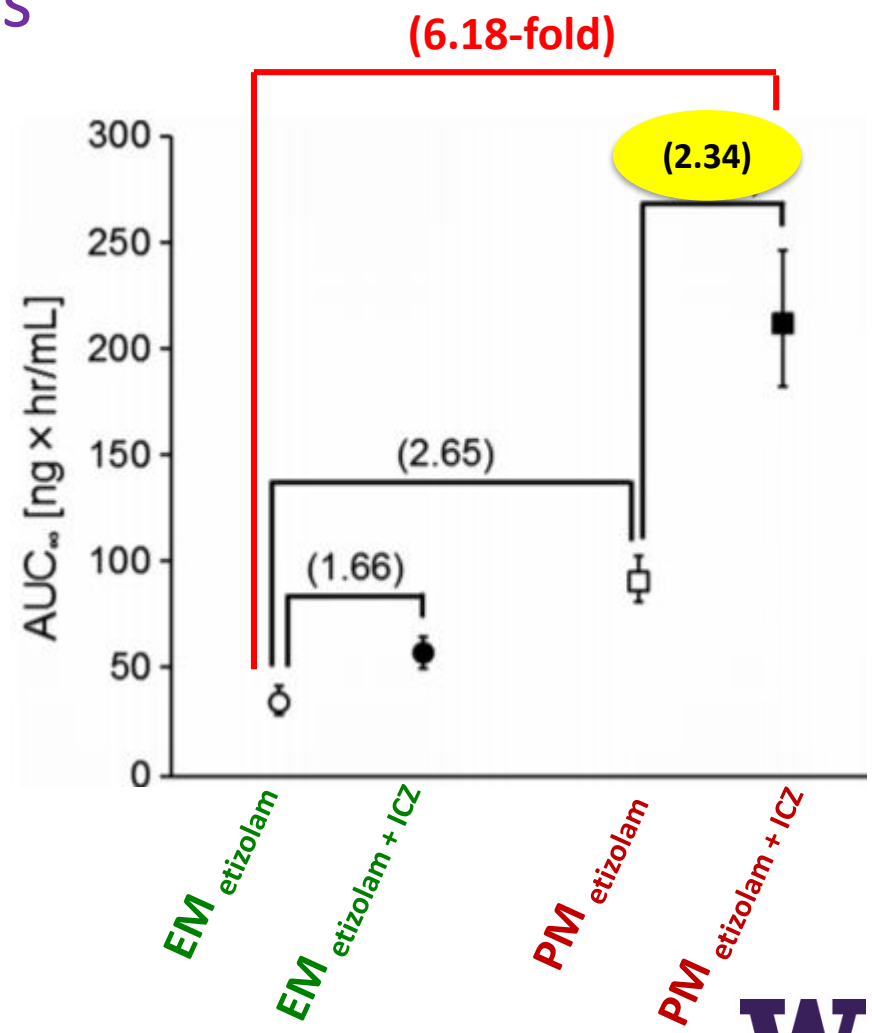
200 mg twice daily (9:00 am and 9:00 pm) on Days 2-5

J Clin Pharmacol. 2017 Nov;57(11):1491-1499.

DDI Between Etizolam and Itraconazole in CYP2C19 Poor Metabolizers

Results





Predicted magnitude of AUC increase in PMs (2.5-fold) consistent with the observed increase *in vivo*.

Itraconazole exposure similar between EM and PM
Etizolam intestinal availability similar between EM and PM

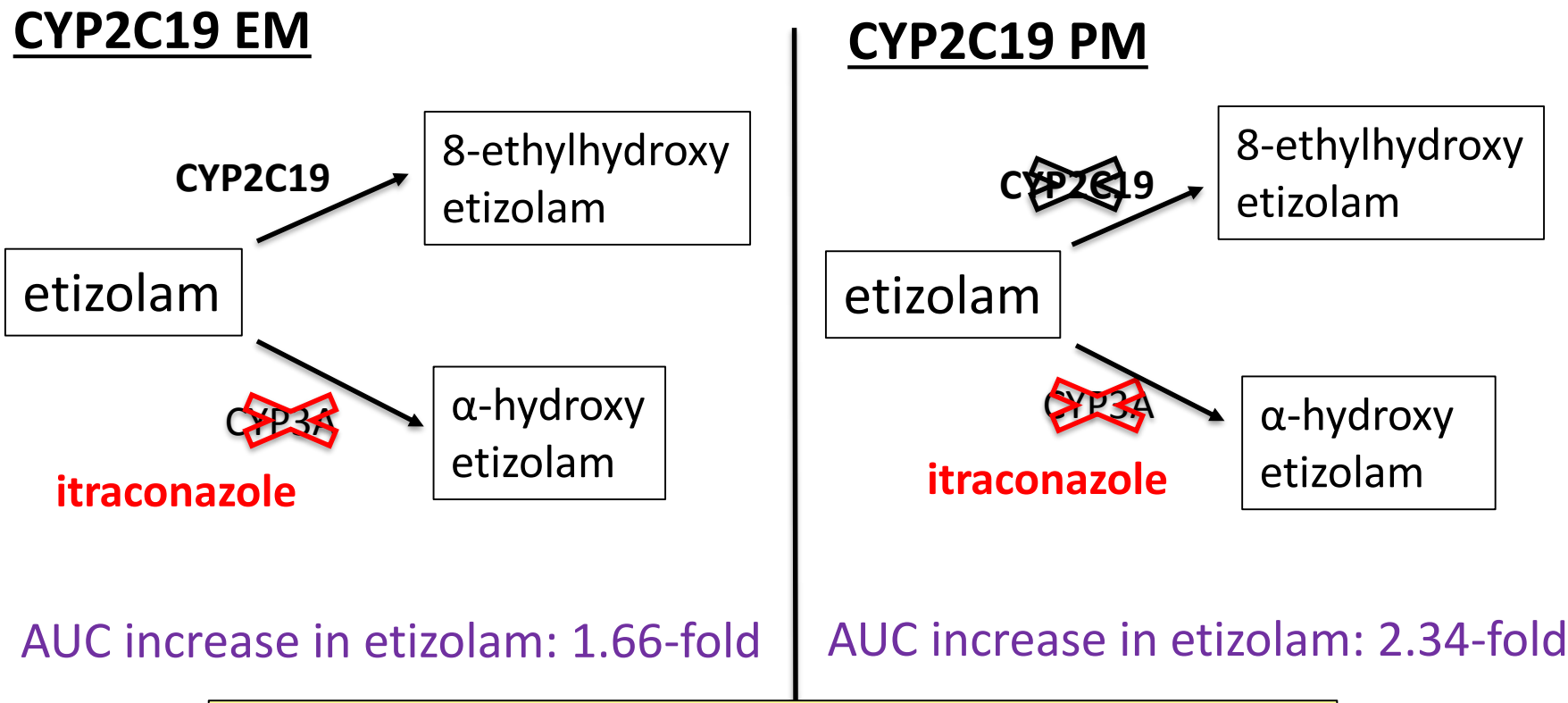
J Clin Pharmacol. 2017 Nov;57(11):1491-1499.

Authors' Conclusion

- Magnitude of DDI between etizolam and itraconazole is dependent upon CYP2C19 genotype
- Prediction of the extent of DDI expected in PMs may be determined via *in vitro* measurements of f_m using HLM (or cryopreserved human hepatocytes) from PM donors
- PGx testing of patients may be useful to manage these genotype-dependent DDIs.

Scenarios Where PGx Critically Affects the Extent of DDIs

Inhibition of Secondary Clearance Pathway



AUC increase in etizolam: 1.66-fold

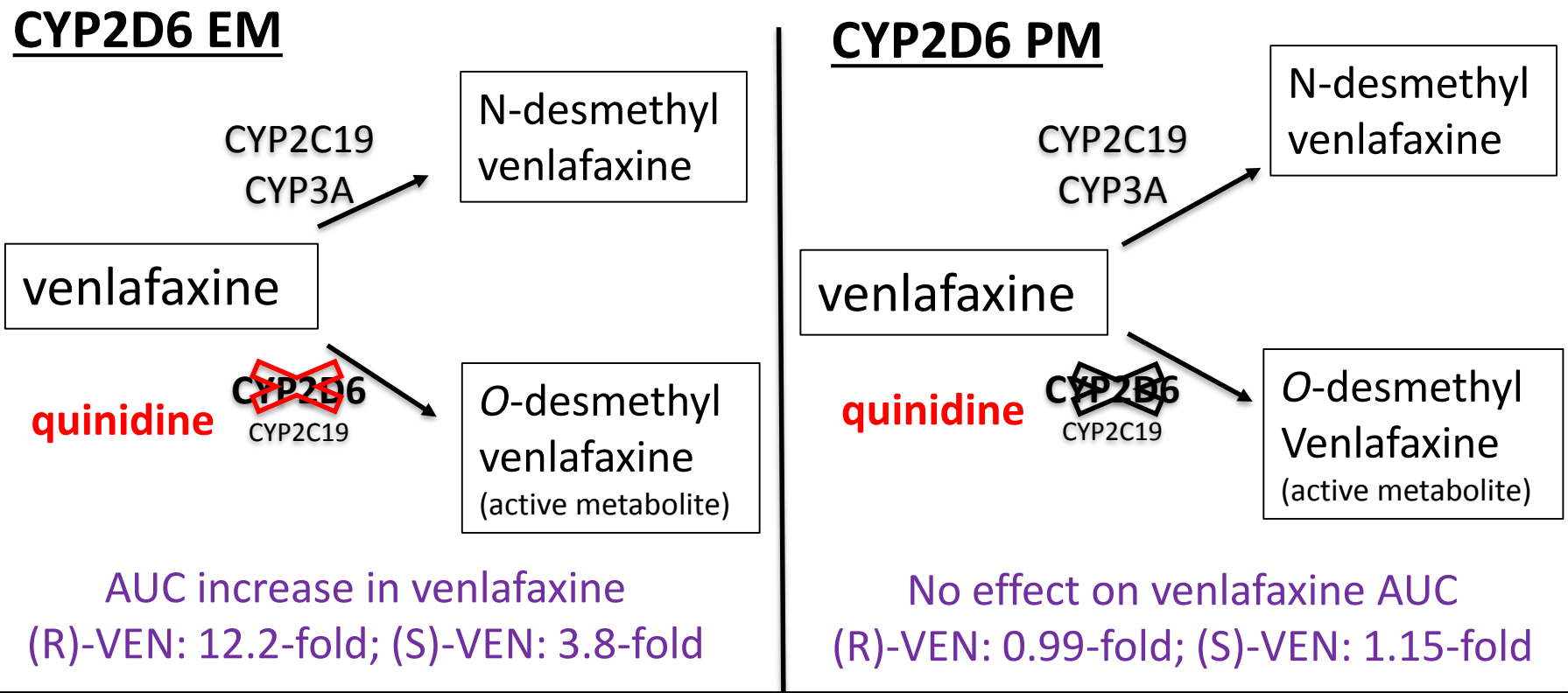
AUC increase in etizolam: 2.34-fold

Maximum increase in etizolam exposure: 6.18-fold
(etizolam administered after the introduction of itraconazole)

J Clin Pharmacol. 2017 Nov;57(11):1491-1499. PMID: 28679023

Scenarios Where PGx Critically Affects the Extent of DDIs

Inhibition of Primary Clearance Pathway



AUC increase in venlafaxine
(R)-VEN: 12.2-fold; (S)-VEN: 3.8-fold

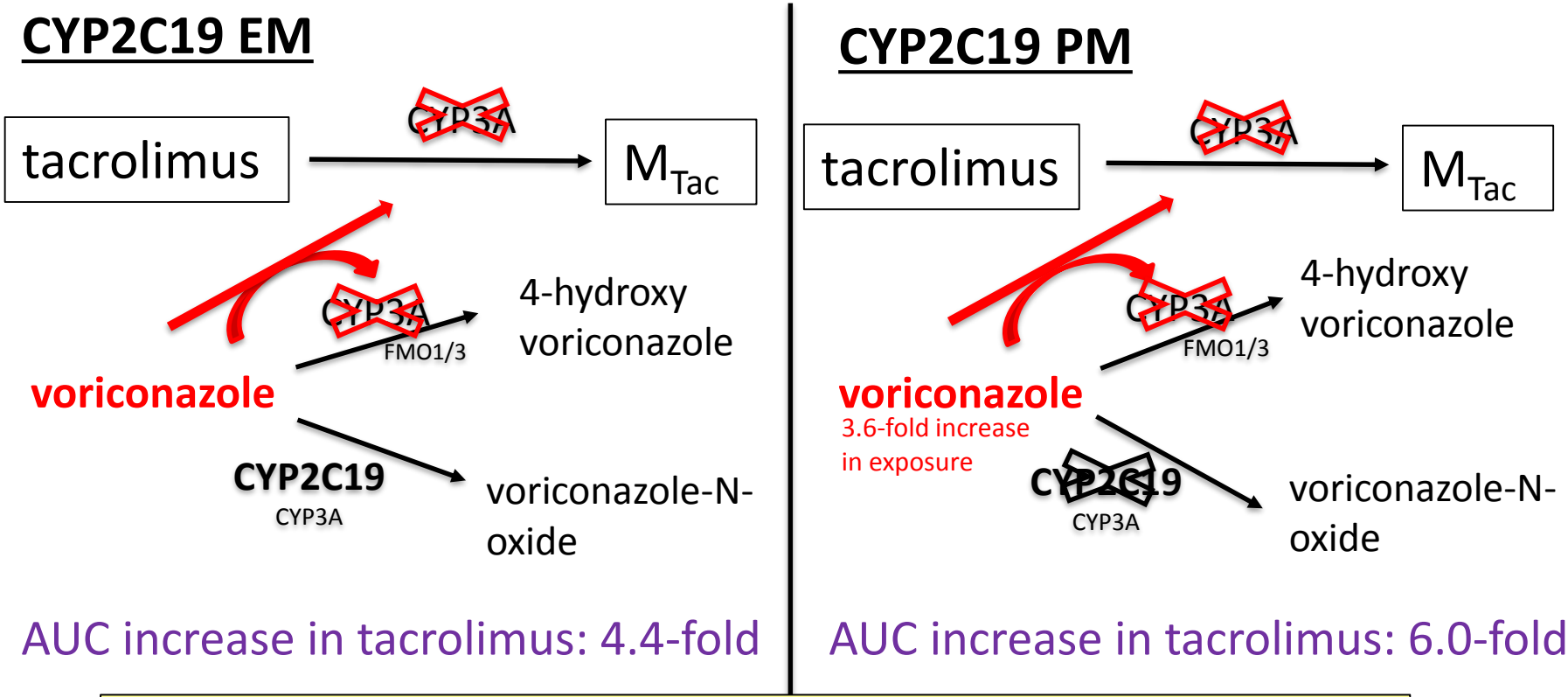
No effect on venlafaxine AUC
(R)-VEN: 0.99-fold; (S)-VEN: 1.15-fold

Maximum increase in venlafaxine exposure: (R)-VEN: 12.2-fold; (S)-VEN: 3.8-fold
(VEN administered after the introduction of quinidine)

Pharmacogenetics. 2003 Jan;13(1):39-47. PMID: 12544511

Scenarios Where PGx Critically Affects the Extent of DDIs

Genotype affects Concentrations of Perpetrator

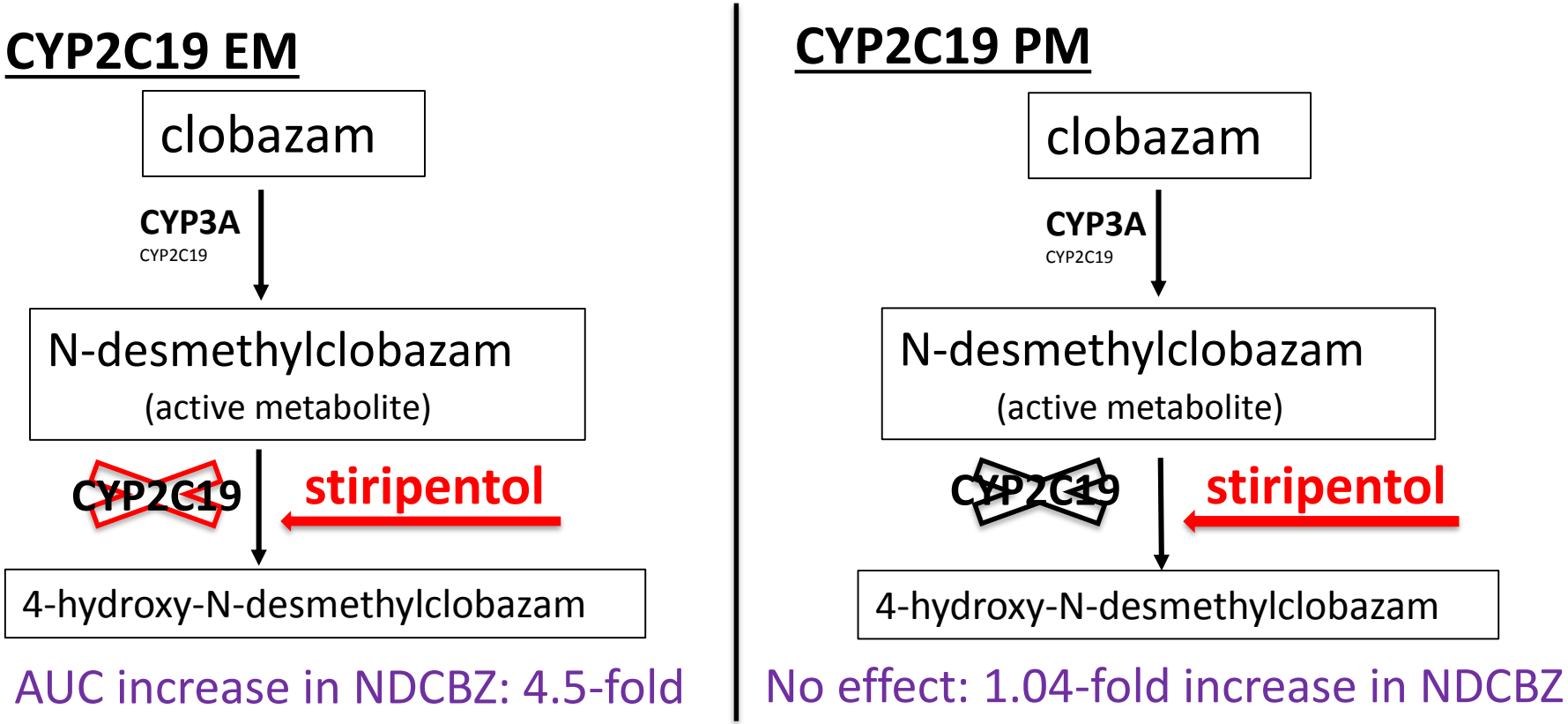


Maximum increase in tacrolimus exposure: 6.5-fold
(tacrolimus administered after the introduction of voriconazole)

J Clin Pharmacol. 2016 Apr;56(4):408-13. PMID: 26239045

Scenarios Where PGx Critically Affects the Extent of DDIs

PGx affects Elimination of Active Metabolite



Maximum increase in N-desmethylclobazam exposure: 15.5-fold
(clobazam administered after the introduction of stiripenthol)

Brain Dev. 2015 Feb;37(2):243-9. PMID: 24819914 [retrospective study]

Example of Gene-Drug-Drug-Interactions (GDDIs)

Conclusions

- Clinical trials evaluating the interplay of gene-drug together with drug-drug interaction are difficult to implement
- GDDIs are often identified via case reports of toxicity
- Both EM and/or PM subjects might be affected by DDI depending on the underlying mechanism
- Extent of the GDDI depends on the timing of the victim first administration relative to the perpetrator
- *In vitro*-based predictions represent a useful tool to evaluate these often complex clinical situations

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Thank you!

Questions?