The Use of BDDCS in Drug Development: The Observations, The Predictions, Understanding the Scientific Basis and The Extensions

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La Jolla **April 19, 2016**

In the early 1990s our group carried out interaction studies in humans with cyclosporine, tacrolimus and sirolimus with and without ketoconazole, an inhibitor of CYP3A and P-gp, as well as with and without rifampin, an inducer of CYP3A and P-gp. These studies suggest that the major effect of the interaction is on bioavailability, as opposed to clearance, and that this interaction occurs primarily in the intestine.

CYP3A and P-glycoprotein

Bioavailability of cyclosporine with concomitant rifampin administration is markedly less than predicted by hepatic enzyme induction

Mary F. Hebert, PharmD, John P. Roberts, MD, Thomayant Prueksaritanont, PhD, and Leslie Z. Benet, PhD *San Francisco, Calif.*

(Clin Pharmacol Ther 1992; 52:453-7)

Differentiation of absorption and first-pass gut and hepatic metabolism in humans: Studies with cyclosporine

Chi-Yuan Wu, MS, Leslie Z. Benet, PhD, Mary F. Hebert, PharmD, Suneel K. Gupta, PhD, Malcolm Rowland, PhD, Denise Y. Gomez, PharmD,[a] and Vincent J. Wacher, PhD
San Francisco, Palo Alto, and Menlo Park, Calif., and Manchester, England

(Clin Pharmacol Ther 1995;58:492-7)

MOLECULAR CARCINOGENESIS 13:129–134 (1995)

WORKING HYPOTHESIS

Overlapping Substrate Specificities and Tissue Distribution of Cytochrome P450 3A and P-Glycoprotein: Implications for Drug Delivery and Activity in Cancer Chemotherapy

Vincent J. Wacher, Chi-Yuan Wu, and Leslie Z. Benet[1]

Department of Pharmacy, University of California, San Francisco, California

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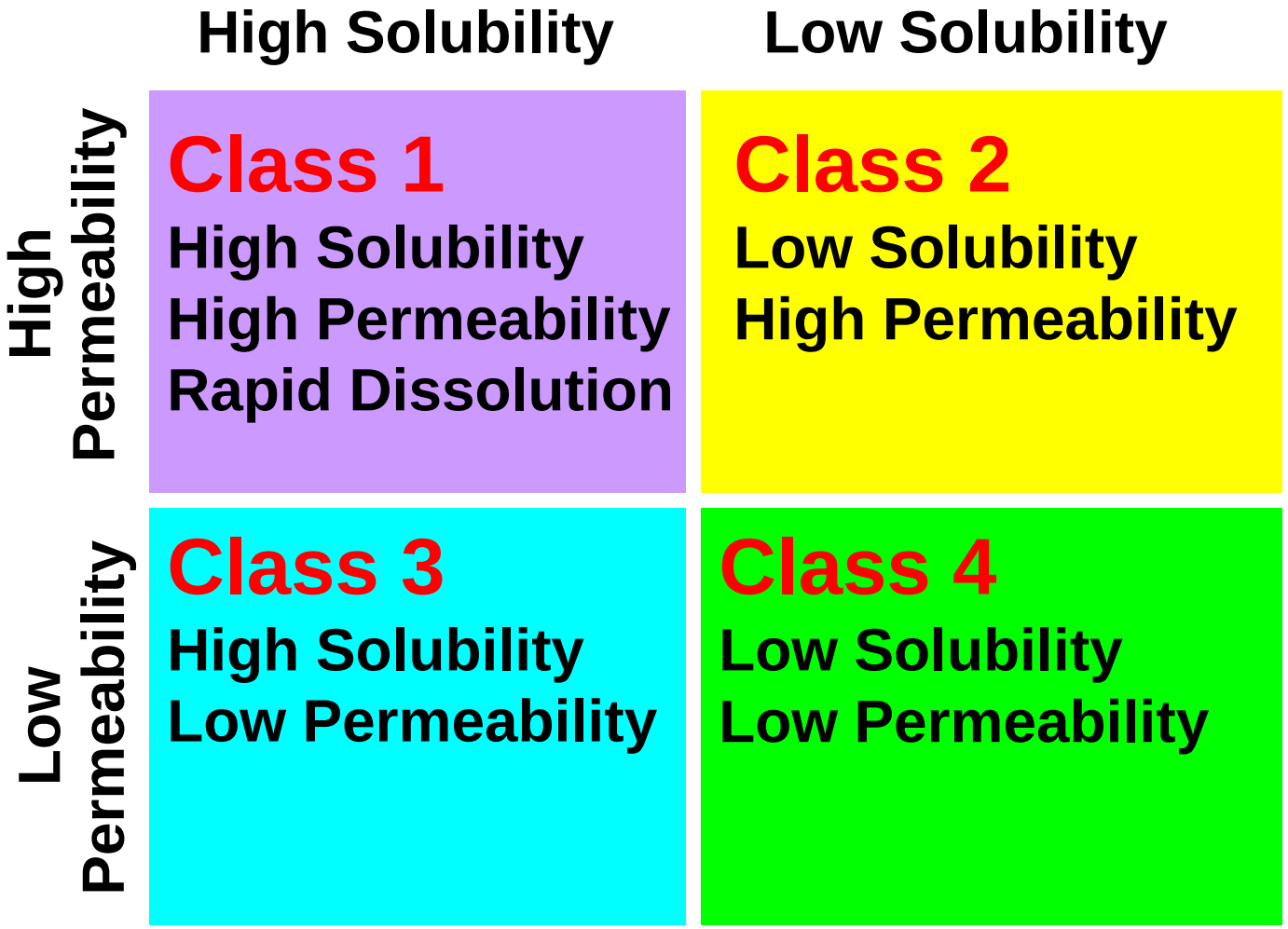
This and the fact that I had been invited to initiate and continue the Appendix on Pharmacokinetic Data in the 1980, 1985, 1990 and 1996 editions of *Goodman and Gilman* then led to development of BDDCS.

Is there a SCDMDG pharmaceutical scientist that is not familiar with BCS?

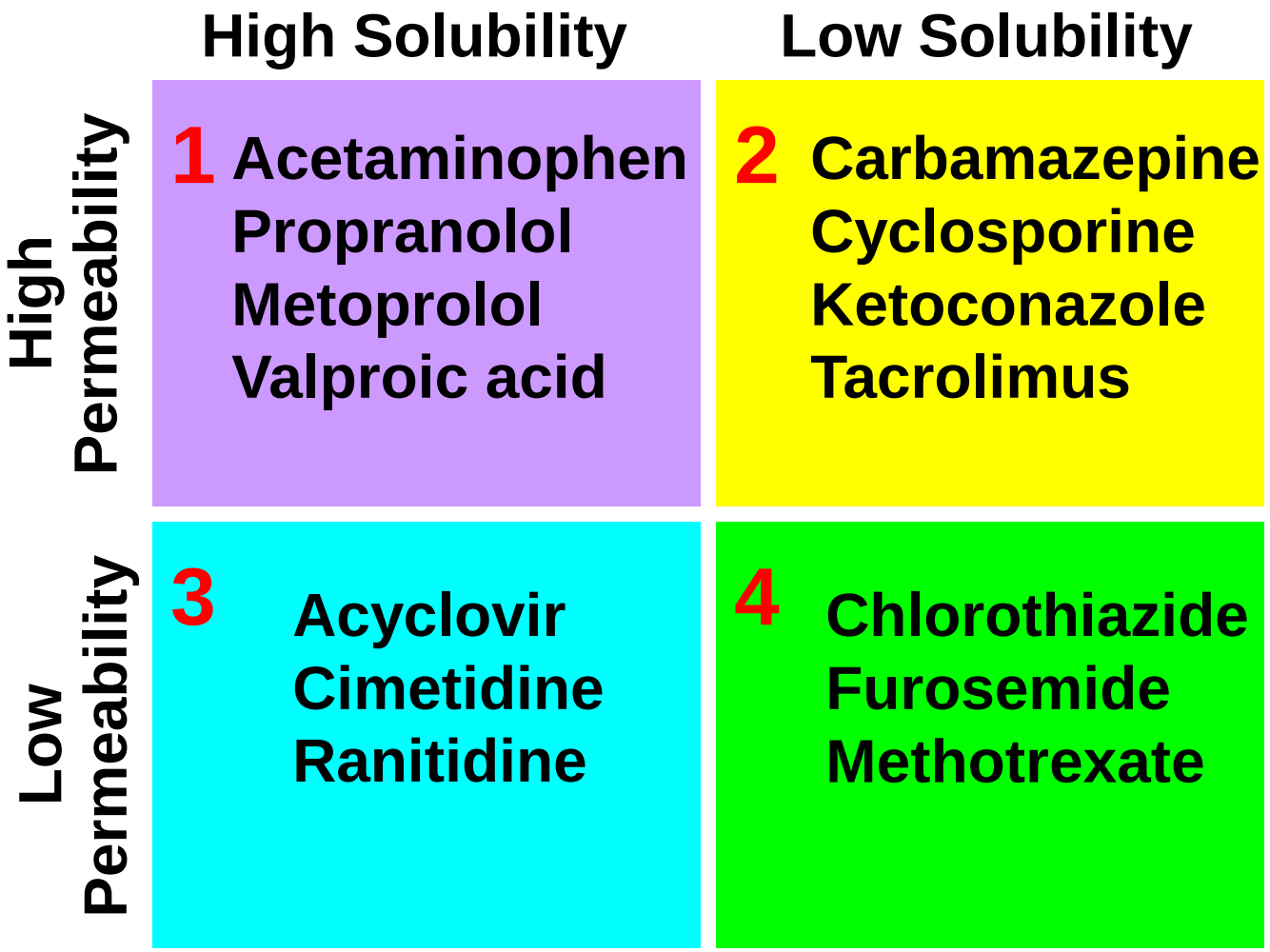
Biopharmaceutics Classification System



Amidon et al., Pharm Res 12: 413-420, 1995

Sample Drugs in Each BCS Class

Biopharmaceutical Classification



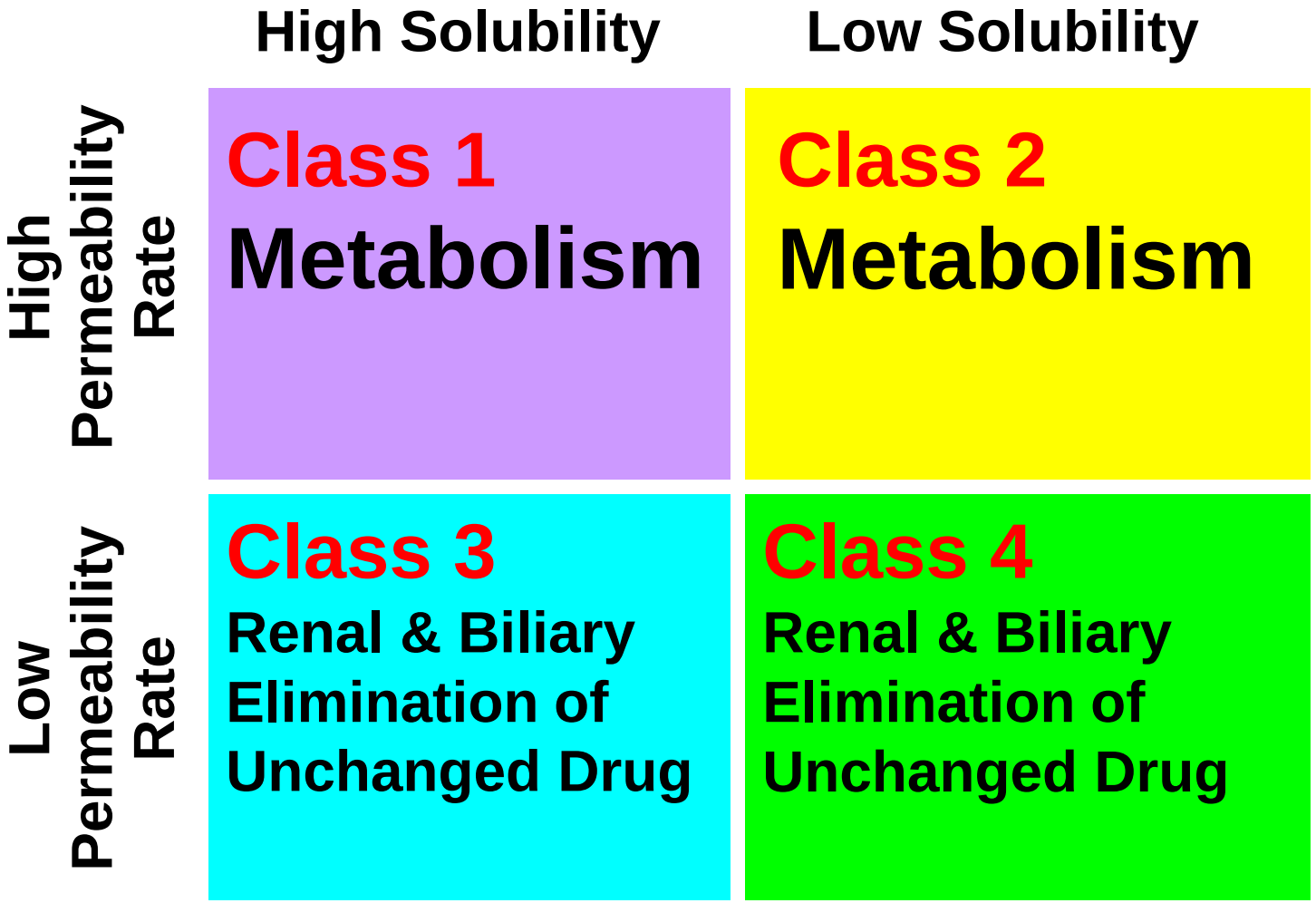
Amidon et al., Pharm Res 12: 413-420, 1995

In the early 2000s, I listened to many BCS presentations and began to realize, based on my *Goodman & Gilman* understanding of drug metabolism/pharmacokinetics, that certain previously unrecognized drug disposition properties were inherent in the BCS system.

Wu and Benet reported in 2005 that for drugs exhibiting high intestinal permeability rates the major route of elimination in humans was via metabolism, while drugs exhibiting poor intestinal permeability rates were primarily eliminated in humans as unchanged drug in the urine and bile.

Major Routes of Drug Elimination

(the very simple discovery)



Wu and Benet, Pharm. Res. **22**: 11-23 (2005)

High passive membrane permeability almost universally results in extensive metabolism in humans

But extensive metabolism in humans does not always correlate with high membrane permeability

“Highly permeable drugs, especially those with permeability rates greater than metoprolol are very likely to require metabolic elimination (97 ± 5% in 20 data sets), and while extensively metabolized drugs tend to be more highly permeable than poorly metabolized drugs, high permeability rate may not be required for a compound to be metabolized.”

Hosey and Benet, Mol Pharmaceut., 2015, 12:1456-1466.

Biopharmaceutics Drug Disposition Classification System

BDDCS

	High Solubility	Low Solubility
Extensive Metabolism	**Class 1** High Solubility Extensive Metabolism	**Class 2** Low Solubility Extensive Metabolism
Poor Metabolism	**Class 3** High Solubility Poor Metabolism	**Class 4** Low Solubility Poor Metabolism

Wu and Benet, Pharm. Res. **22**: 11-23 (2005)

What is the Basis for the Discovery?

The recognition of the correlation between intestinal permeability rate and extent of metabolism preceded an explanation for these findings. That is, why should intestinal permeability rate predict the extent of metabolism?

We now suspect that high permeability rate compounds are readily reabsorbed from the kidney lumen and from the bile facilitating multiple access to the metabolic enzymes. In essence the only way the body can eliminate these compounds is via metabolism. This would explain why drugs with quite low hepatic clearance are still completely eliminated by metabolism (e.g., diazepam).

A confusion in BCS relates to whether the term permeability is an extent measure or a rate measure. As stated in the FDA guidance a "highly permeable" compound is based on the extent of absorption. However, the FDA, but not the EMA, also allow BCS classification to be based on intestinal permeability rate. Why?

Initially, based on a limited number (34) of compounds for which human *in vivo* intestinal permeability rate measures were experimentally determined, the correlation between permeability rate and extent of absorption held reasonably well.

But that is no longer true.

The FDA has classified as "highly permeable" a number of drugs where absorption is ≥ 90% in humans, but the permeability rate of these compounds is less than that for metoprolol and in at least one case* less than mannitol.

These drugs include cefadroxil, cephradine, levofloxacin, loracarbef, ofloxacin, pregabalin* and sotalol.

Chen and Yu, Mol. Pharmaceut. 6:74-81 (2009)

Major Differences Between BDDCS and BCS

- **Purpose: BCS – Biowaivers of in vivo bioequivalence studies.**
  BDDCS – Prediction of drug disposition and potential DDIs in the intestine & liver.
- **Criteria: BDDCS – Predictions based on intestinal permeability rate**
  BCS – Biowaivers based on extent of absorption, which in a number of cases does not correlate with jejunal permeability rates

Prediction of Oral Dosing Transporter Effects Based on BDDCS Class

	High Solubility	Low Solubility
High Permeability/ Metabolism	**Class 1** Transporter effects minimal in gut and liver and clinically insignificant	**Class 2** Efflux transporter effects predominate in gut, but both uptake & efflux transporters can affect liver
Low Permeability/ Metabolism	**Class 3** Absorptive transporter effects predominate (but can be modulated by efflux transporters)	**Class 4** Absorptive and efflux transporter effects could be important

S. Shugarts and L. Z. Benet. Pharm. Res. 26, 2039-2054 (2009).

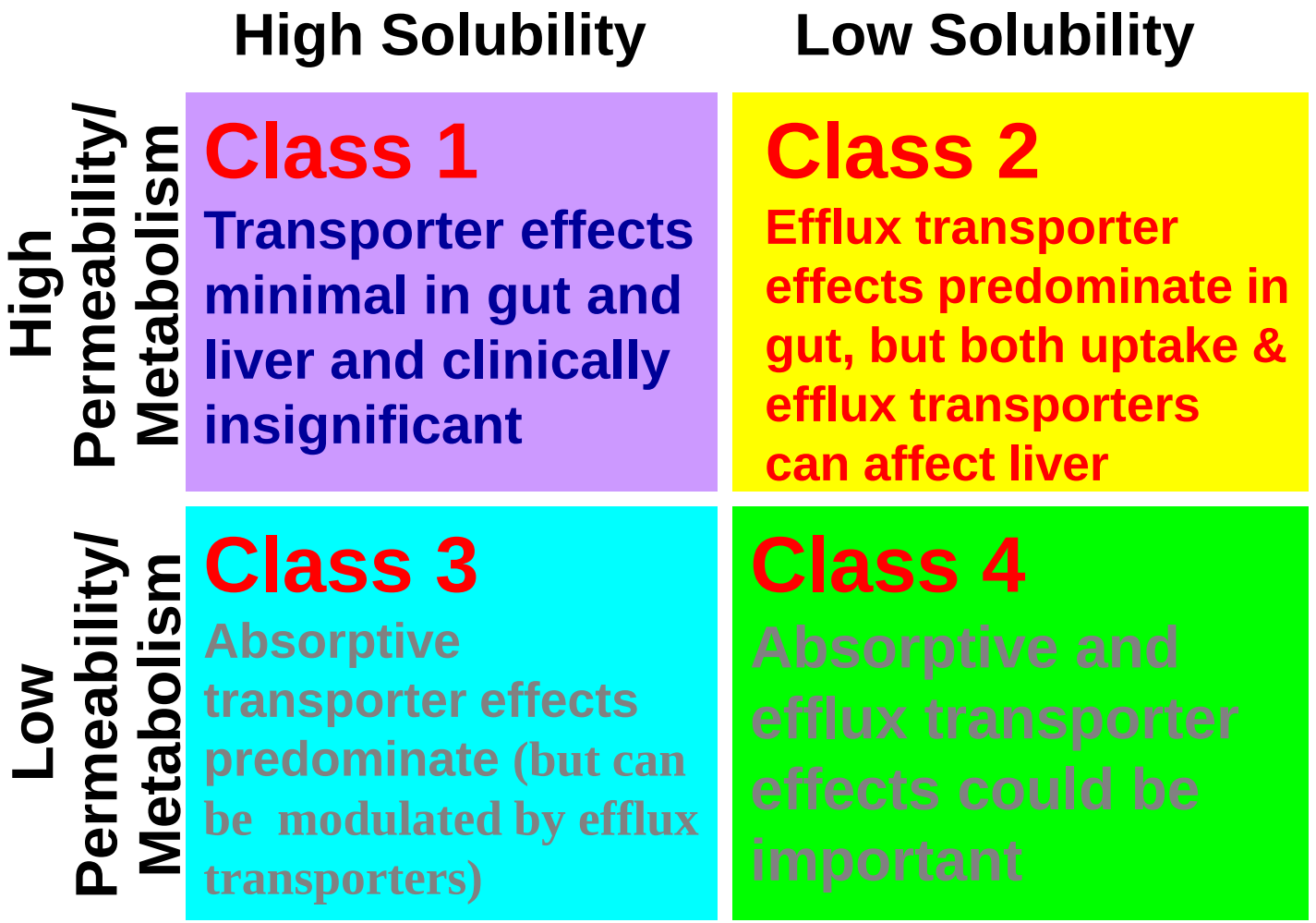
Why Should Solubility Affect Disposition?

US FDA solubility is a property of the drug in a formulation and is not an intrinsic property of the actual pharmaceutical ingredient itself. Some suggest that solubility is a fundamental principal for oral absorption since only drug in solution has the ability to permeate across enterocytes, but it is not directly relevant to drug clearance. Yet, aqueous solubility is an indirect measure of lipophilicity, which is also reflected in membrane permeability.

However, scientists are very poor at predicting solubility. We recently showed that the correlation between measured and predicted minimum solubility yielded an r^2 of no more than 33%, even when the predictions included pH. That is, we don't understand the physics of solubility. Earlier this year, we proposed that for highly soluble drugs, where concentrations are not limited by solubility, active processes may occur but they are overwhelmed by passive permeability.

Reliability of In Vitro and In Vivo Methods for Predicting the Effect of P-Glycoprotein on the Delivery of Antidepressants to the Brain. Y. Zheng, X. Chen and L. Z. Benet. Clin. Pharmacokinet. 55, 143-167 (2016).

Prediction of Oral Dosing Transporter Effects Based on BDDCS Class



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What about the lipophilicity/solubility characteristics of the drugs in the various BDDCS classes? Can they be predicted using *in silico* methodology?

We tried to address this question by compiling, as I had done previously for PK in Goodman & Gilman, the relevant measured and here *in silico* parameters.

BDDCS Applied to Over 900 Drugs

L. Z. Benet, F. Broccatelli, and T. I. Oprea

AAPS Journal 13: 519-547 (2011)

Oral Drugs

Higher PSAD

Lower PSAD

Class 1		
cLogP	minVSLgS	ALOGPS
2.47 ± 2.12	-2.42 ± 1.71	-3.42 ± 1.40
MW	PSA	PSAD
323.8 ± 123.3	66.0 ± 50.9	18.1 ± 44.7

Class 2		
cLogP	minVSLgS	ALOGPS
3.79 ± 2.08	-4.07 ± 1.72	-4.26 ± 1.12
MW	PSA	PSAD
385.0 ± 144.3	75.3 ± 44.6	9.4 ± 23.7

Class 3		
cLogP	minVSLgS	ALOGPS
-0.05 ± 2.01	-0.82 ± 2.14	-2.55 ± 1.30
MW	PSA	PSAD
329.8 ± 185.2	107.1 ± 75.9	3.6 ± 1.8

Class 4		
cLogP	minVSLgS	ALOGPS
1.65 ± 2.67	-2.37 ± 2.31	-3.45 ± 1.18
MW	PSA	PSAD
394.6 ± 170.7	113.1 ± 42.7	3.8 ± 1.6

cLogP

minVSLgS

Lower MW

Higher MW

It is important to recognize that the BDDCS characterization of transporter effects, and transporter enzyme interplay do not predict that every drug in each Class will display the effects listed.

Rather BDDCS predicts what transporter effects may occur, and which may not, and what should be tested.

For the 153 drugs classified in the BDDCS system by Wu and Benet in 2005, we were unable to identify any clinically relevant transporter effects for Class 1 drugs.

Yet, Wu and Benet caution that one "should expect to find exceptions for such a simple 4 category system". As we expand BDDCS classification now to more than 1100 drugs, Varma et al. have recently reported what they believe to be two Class 1 exceptions, cerivastatin and fluvastatin, that exhibit relevant OATP hepatic uptake effects.

Varma et al. Pharm. Res. 32: 3785-3802 (2015)

As noted, Varma et al. recently suggested that two statins, fluvastatin and cerivastatin, classified as BDDCS Class 1, do exhibit rate limited uptake into hepatocytes as a function of OATPs. But, their suggestion is not supported, and is in fact contradicted, by clinical data. Niemi and co-workers report that OATP1B1 polymorphisms that have been shown to affect the pharmacokinetics of all of the BDDCS Classes 2, 3 and 4 statins, do not affect the pharmacokinetics of the BDDCS Class 1 statin, fluvastatin. Cerivastatin was removed from the market before any such evaluation was carried out. Varma et al. have fallen into the trap noted in the earlier slide concerning transporter effects on orally administered drugs; BDDCS Class 1 compounds can be shown to be substrates of transporters, but these transporter effects are clinically insignificant.

Varma et al. Predicting Clearance Mechanism in Drug Discovery: Extended Clearance Classification System. Pharm. Res. 32: 3785-3802 (2015)

Niemi et al. *SLCO1B1* Polymorphism and Sex Affect the Pharmacokinetics of Pravastatin But Not Fluvastatin. Clin. Pharmacol. Ther. 80, 356-366 (2006).

Kalliokoski & Niemi. Impact of OATP Transporters on Pharmacokinetics. Br. J. Pharmacol. 158, 693-705 (2009).

There are a number of very useful observations in Varma et al. "Predicting Clearance Mechanisms in Drug Discovery: Extended Clearance Classification System (ECCS)", but we find it to be too limited and having many more exceptions than BDDCS.

For example, no drugs with MW >700 are considered, the system does not predict the importance of gut metabolism or disposition of prodrugs, ionization state is given more significance than justified, and biliary excretion is not addressed except for drugs rate limited by hepatic uptake.

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Predicting when Biliary Excretion of Parent Drug is the Major Route of Elimination in Humans

Chelsea M. Hosey, Fabio Broccatelli, and Leslie Z. Benet

AAPS Journal
16: 1085-1096 (2014)

One of the great difficulties in defining drug disposition relates to NMEs that are primarily eliminated unchanged in bile in humans. Previous studies have recommended that high molecular weight compounds may follow this route. But many Class 1 and 2 drugs that are primarily eliminated by metabolism meet the proposed MW cut-offs. Only 12% of orally administered drugs with MW>380 Da are biliarily eliminated.

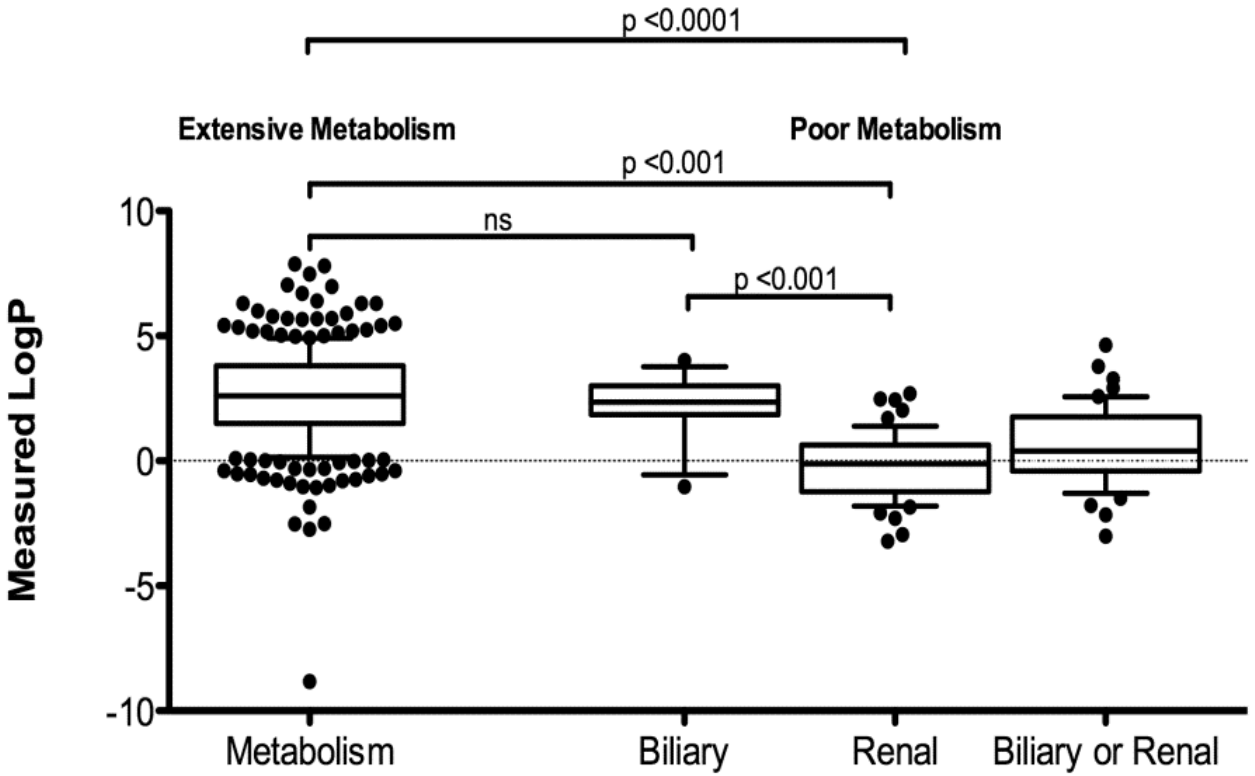
Table III. Population of Compounds in Molecular Weight Groups by Route of Administration and Elimination

	Molecular weight (Da)			
	>380	<380	>475	<475
Major elimination route	Oral administration			
Biliary	22	5	13	14
Renal	13	65	0	78
Metabolism	153	345	53	445
	Non-oral administration			
Biliary	11	1	7	5
Renal	42	21	21	42
Metabolism	42	50	29	63

87% of orally administered biliarily and metabolized compounds with MW > 380 Da are metabolized, and 80% of orally administered biliarily and metabolized compounds with MW > 475 Da are metabolized.

Hosey et al., AAPS J., 2014,16:1085-1096.

Measured Log P *vs* Elimination Route



Hosey et al., AAPS J., 2014,16:1085-1096.

Hosey et al. reported that for a data set of 105 orally administered BDDCS Class 3 and 4 drugs, 27 significantly excreted in the bile and 78 primarily excreted in the urine (29 anionic, 26 cationic, 33 neutral and 17 zwitterionic at pH 7.5), 2 *in silico* parameters, polarizability and metabolic stability calculated in VolSurf+, were 92.5 ± 0.1% accurate in 10x5 fold cross-validation and was more accurate ($p<0.01$) than other models we tested in predicting biliary vs renal elimination.

[Sensitivity 0.90±0.10, Specificity 0.93±0.06, PPV 0.84±0.0.12, NPV 0.97±0.04]

Potential DDIs Predicted by BDDCS

- Class 1: Only metabolic in the intestine and liver
- Class 2: Metabolic, efflux transporter and efflux transporter-enzyme interplay in the intestine. Metabolic, uptake transporter, efflux transporter and transporter-enzyme interplay in the liver.
- Class 3 and 4: Uptake transporter, efflux transporter and uptake-efflux transporter interplay

The Use of BDDCS for Drugs on the Market

- Predict potential drug-drug interactions not tested in the drug approval process
- Predict the potential relevance of transporter-enzyme interplay
- Assist the prediction of when and when not transporter and/or enzyme pharmacogenetic variants may be clinically relevant
- Predict when transporter inhibition of uremic toxins may change hepatic elimination
- Predict the brain disposition
- Increase the eligibility of drugs for BCS Class 1 biowaivers using measures of metabolism

Oral Dosing Transporter Effects

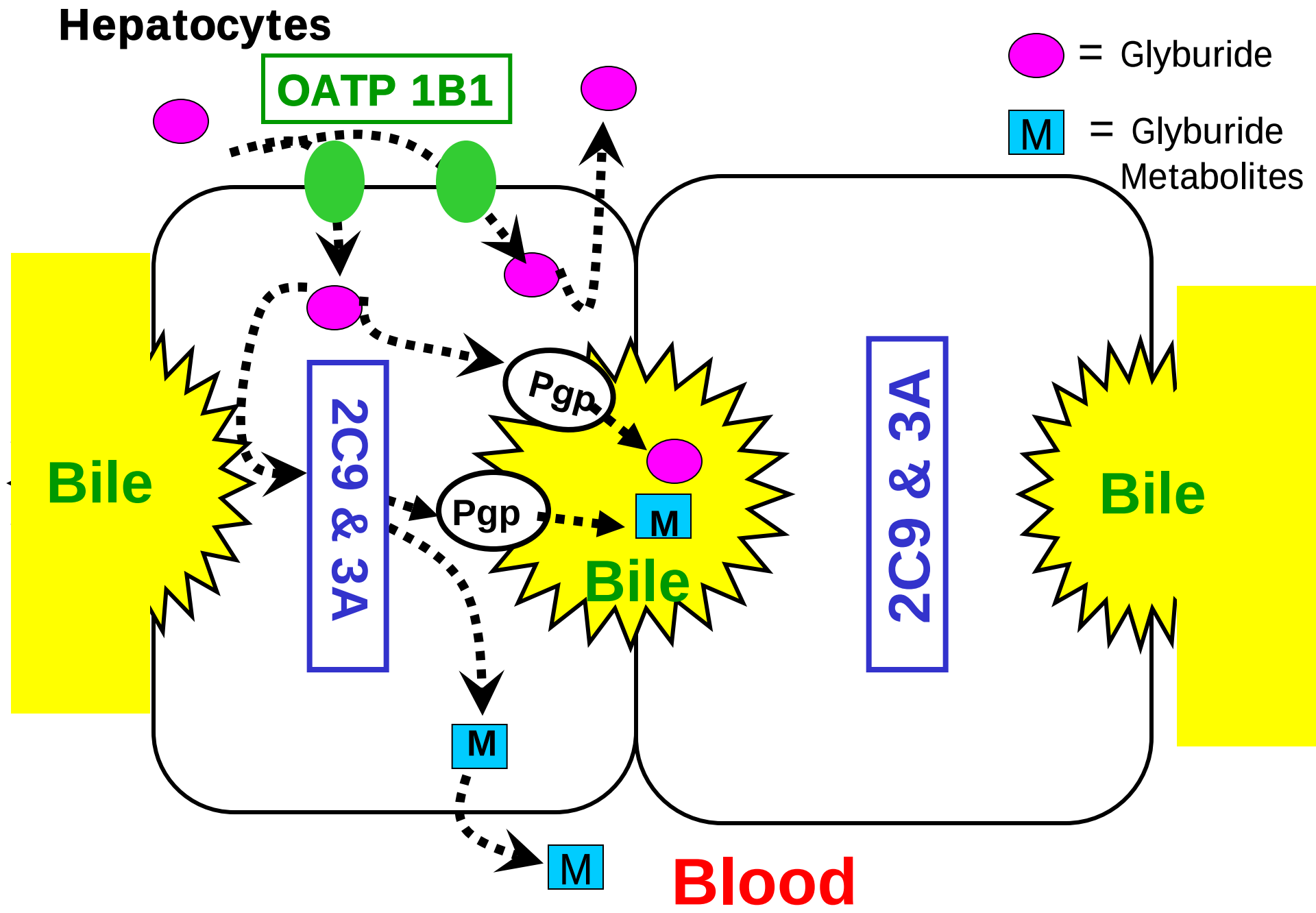
	High Solubility	Low Solubility
High Permeability/ Metabolism	**Class 1** Transporter effects minimal in gut and liver	**Class 2** Efflux transporter effects predominate in gut, but both uptake & efflux transporters can affect liver
Low Permeability/ Metabolism	**Class 3** Absorptive transporter effects predominate (but can be modulated by efflux transporters)	**Class 4** Absorptive and efflux transporter effects could be important

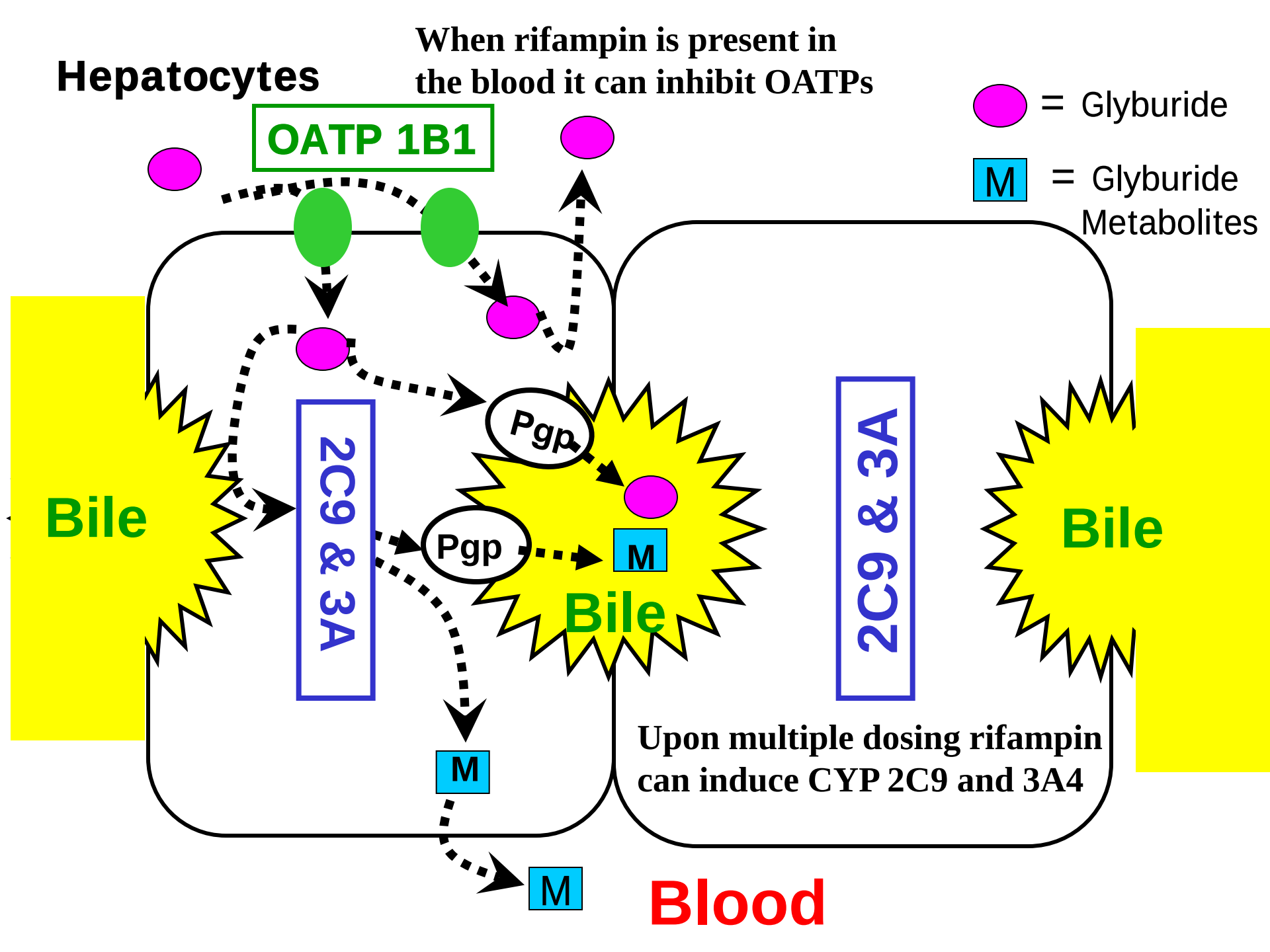
Elucidating Rifampin's Inducing and Inhibiting Effects on Glyburide Pharmacokinetics and Blood Glucose in Healthy Volunteers: Unmasking the Differential Effect of Enzyme Induction and Transporter Inhibition for a Drug and Its Primary Metabolite

HongXia Zheng, Yong Huang, Lynda Frassetto, and Leslie Z. Benet

Clinical Pharmacology & Therapeutics

85:78-85 (2009)


Hepatocytes
OATP 1B1
= Glyburide
M = Glyburide Metabolites
Bile
2C9 & 3A
Pgp
Pgp
M
Bile
2C9 & 3A
Bile
M
M
Blood


Hepatocytes
When rifampin is present in the blood it can inhibit OATPs
OATP 1B1
= Glyburide
M = Glyburide Metabolites
Bile
2C9 & 3A
Pgp
Pgp
M
Bile
2C9 & 3A
Bile
M
M
Upon multiple dosing rifampin can induce CYP 2C9 and 3A4
Blood

Study Design

Effects of Single IV Rifampin (RIF) on Glyburide

Ten Healthy Volunteers

Visit 1
Day 1

Glyburide 1.25mg P.O.
(PK Study)

Visit 2
Day 8

Rifampin 600mg I.V.
Glyburide 1.25mg P.O.
(PK Study)

Study Design (Continued)
Inhibition and Induction Effects of RIF on Glyburide

ALL Healthy Volunteers

↓

Rifampin 600mg P.O. for 6 days

↓

Visit 3
Day 15

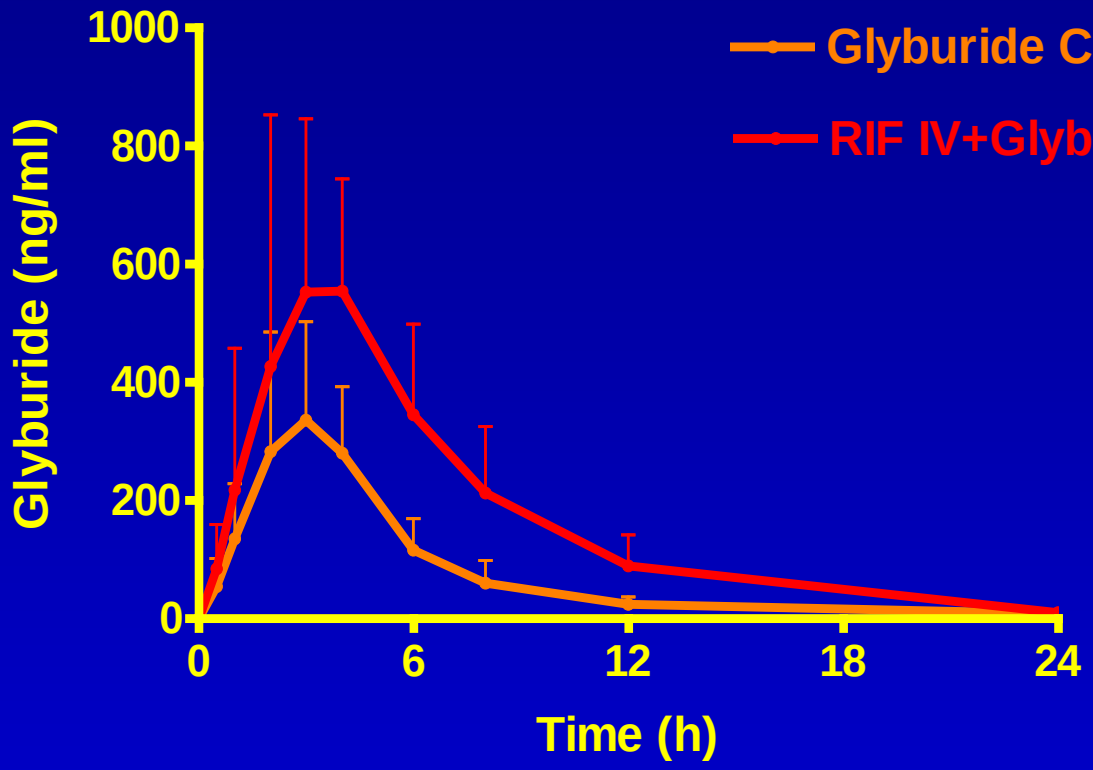
Rifampin 600mg I.V.
Glyburide 1.25mg P.O.
(PK study)

↓

Visit 4
Day 17

Glyburide 1.25mg P.O.
(PK study)

Inhibition of Glyburide Uptake by IV RIF



C_{max} 81% ↑ *

$T_{1/2}$ 31% ↓ *

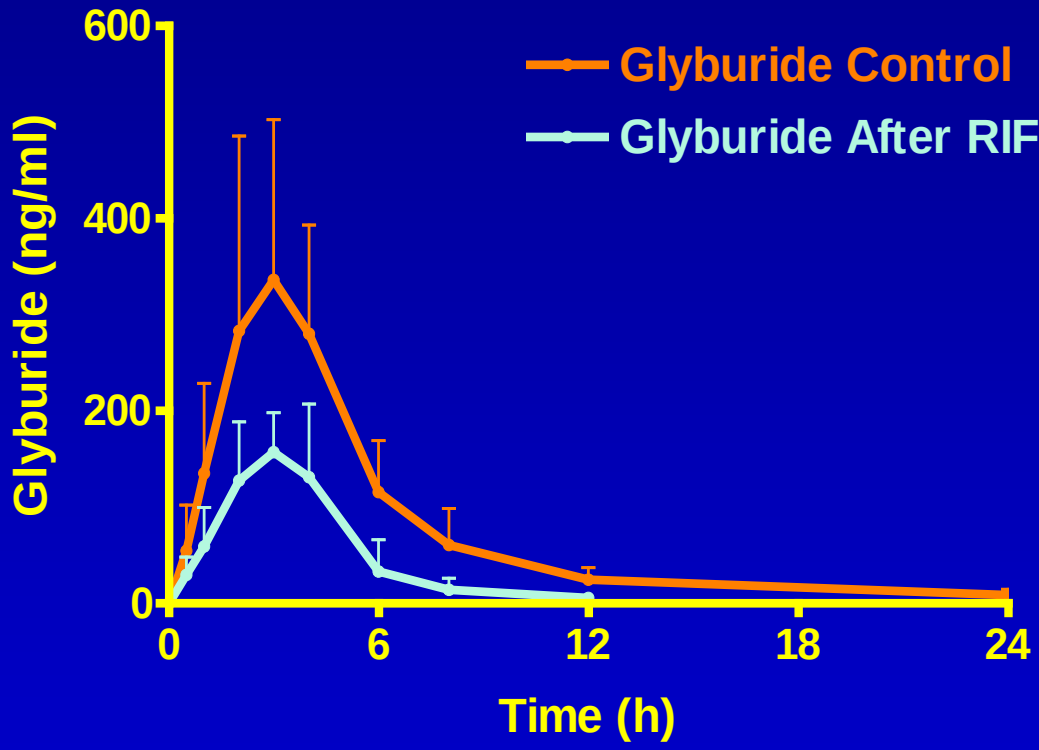
$AUC_{0\text{-}inf}$ 125% ↑ *

CL/F 53% ↓ *

V_{ss}/F 60% ↓ *

* P<0.05

CYP450 Induction Effect on Glyburide When No RIF Present in the Plasma



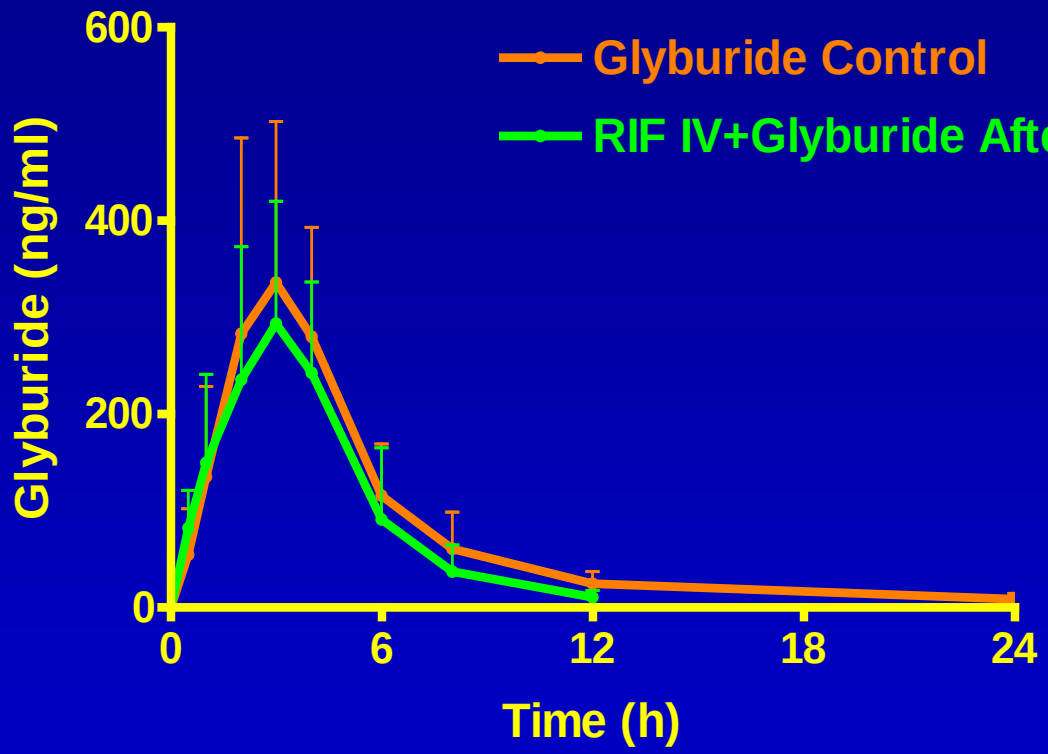
C_{max} 48% ↓ *

$AUC_{0\text{-}inf}$ 63% ↓ *

CL/F 197% ↑ *

V_{ss}/F 32% ↑ ns

Uptake Inhibition and CYP450 Induction Effects on Glyburide When RIF Present in the Plasma



C_{max} 9% ↓

$AUC_{0\text{-}inf}$ 22% ↓*

CL/F 37% ↑*

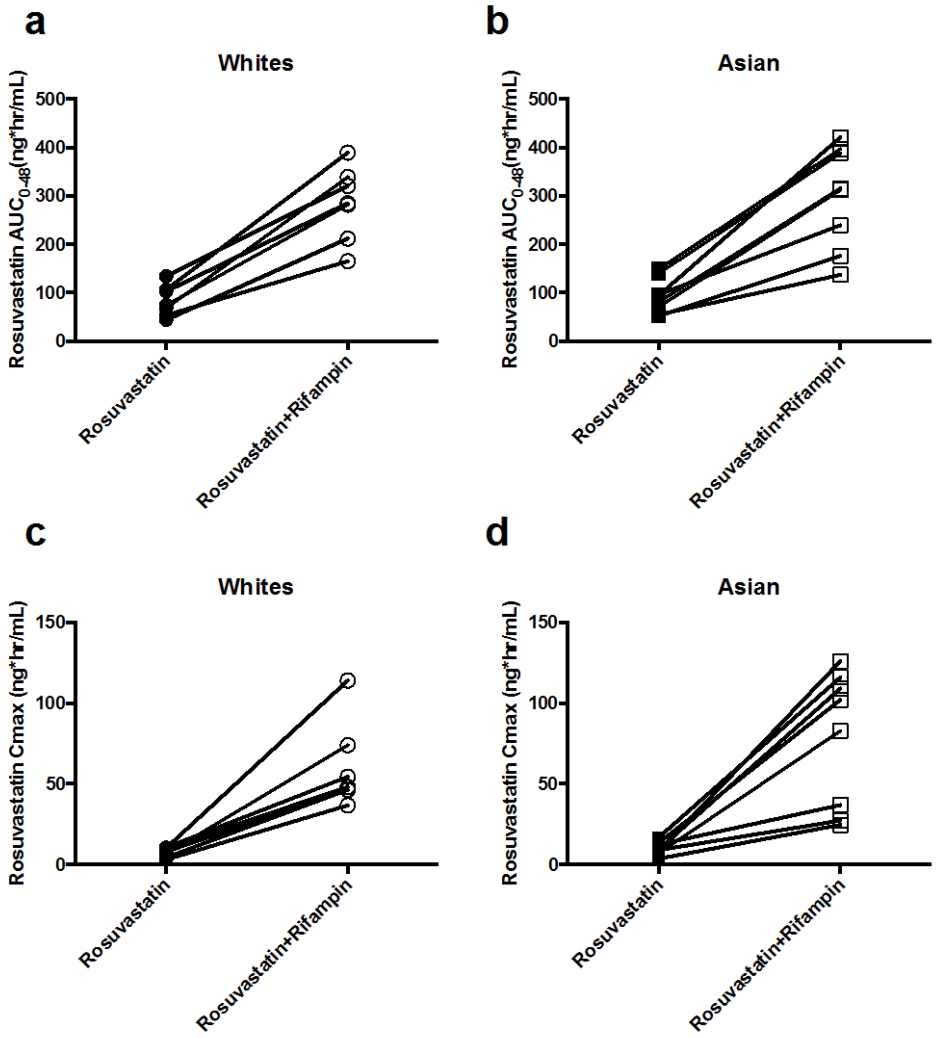
V_{ss}/F 43% ↓*

Precision medicine dosing of rosuvastatin should be preferentially based on genotype rather than ethnicity

Hsin-Fang Wu, Nadya Hristeva, Jae Chang, Xiaorong Liang, Ruina Li, Lynda Frassetto and Leslie Z. Benet

Submitted for publication February 26, 2016

The effect of rifampin on the pharmacokinetics of rosuvastatin in White and Asian healthy volunteers, wild-type for both OATP1B1 and BCRP. Rosuvastatin AUC_{0-48} and C_{max} following a single oral dose of 20 mg rosuvastatin, with and without the administration of rifampin in (a and c) White and (b and d) Asian subjects.



Pharmacokinetic parameters of rosuvastatin following a 20 mg oral dose of rosuvastatin alone or in combination with 600 mg i.v. rifampin to healthy subjects wild-type in both OATP1B1 and BCRP.

	WHITE Control	ASIAN Control
C_{max} (ng/ml)	7.6 ± 2.8	10.0 ± 3.8
$AUC_{0\rightarrow48}$ (ng • hr/ml)	72.2 ± 31.5	86.2 ± 35.5
CL/F (L/hr)	275 ± 111	247 ± 94
V_{ss}/F (L)	4340 ± 4350	3040 ± 2340
	WHITE Rifampin	**ASIAN Rifampin**
C_{max} (ng/ml)	60.0 ± 24.5	78.1 ± 39.4
$AUC_{0\rightarrow48}$ (ng • hr/ml)	278 ± 73	295 ± 97
CL/F (L/hr)	73.1 ±26.9	77.5 ± 35.4
V_{ss}/F (L)	301 ± 144	331 ± 219

The Use of BDDCS for New Molecular Entities and Its Role in Drug Development

We understand the dilemma faced by the industry and the rationale of Varma et al. in discounting the importance of solubility to predict clearance mechanisms for an NME early in development. Although it is easy to test the passive permeability and determine the major route of elimination, knowing the therapeutic dose and thus the relevant solubility is not possible. Yet, as we have shown, solubility is an important determinant in differentiating dispositional characteristics of Class 2 *vs* Class 1 drugs. In the past, we have recommended following an earlier Pfizer proposal to make a preliminary solubility decision based on a 50 mg dose.

We continue to make this recommendation because as we noted previously:

"BDDCS predicts what transporter effects may occur, and which may not, and what should be tested"

and, as we show most recently, as drug development proceeds BDDCS becomes self-correcting:

"BDDCS Predictions, Self-Correcting Aspects of BDDCS Assignments, BDDCS Assignment Corrections and Classification for More Than 175 Additional Drugs" CM Hosey, R Chan & LZ Benet AAPS J 18, 251-260 (2016).

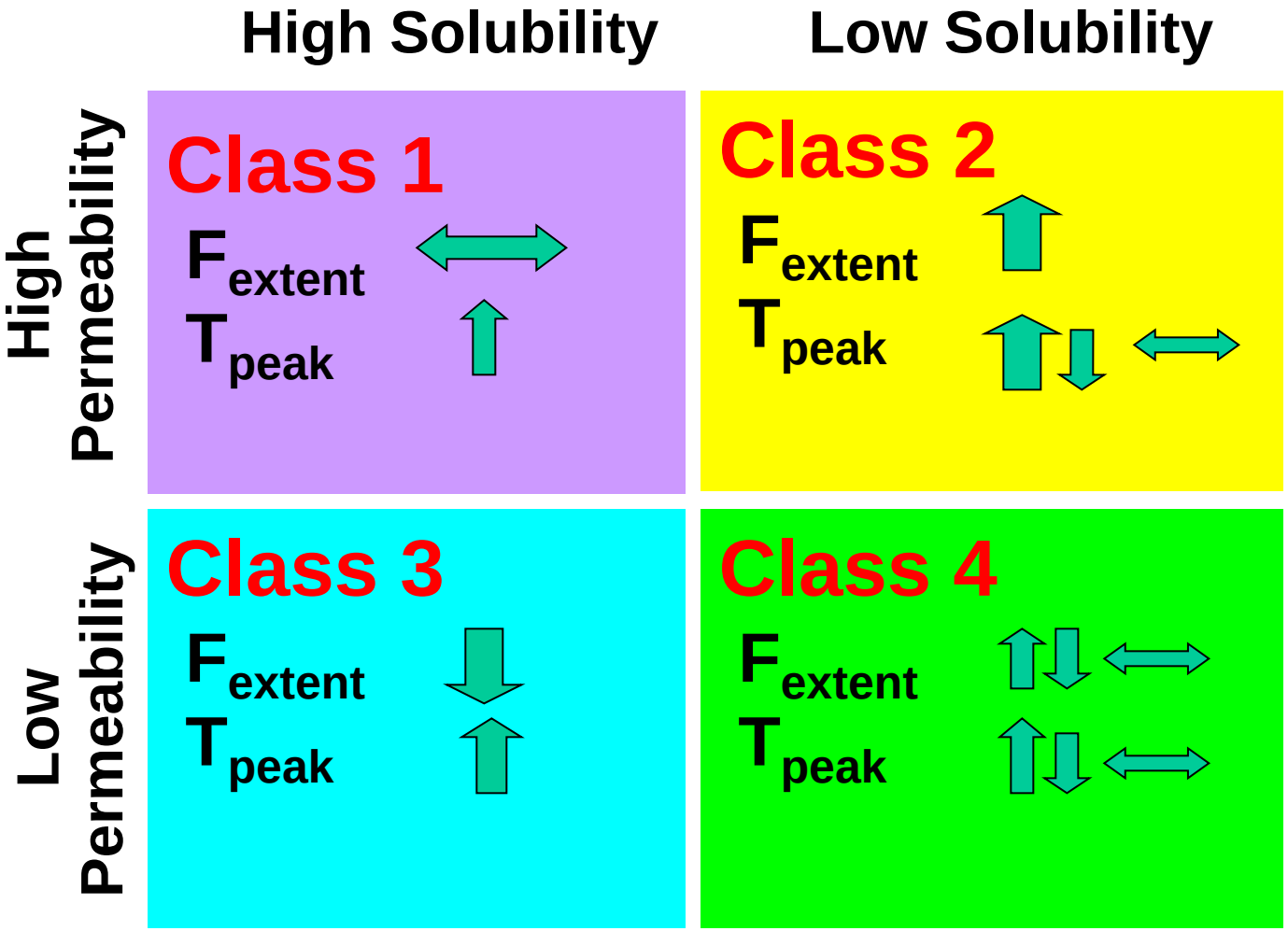
Our latest thinking on solubility

Solubility is a characteristic of a drug substance that subsumes a number of individual characteristics that we and others have not yet been able to identify or quantify that are determinants of drug disposition. Our latest analyses suggest that a 100 mg (or very slightly poorer, 50 mg) in 250 ml water over the pH range 1-6.8 adequately predicts BDDCS class, independent of highest approved dose strength. And that this pH range is important, so we would not reclassify acids that only fail the solubility criteria at pH 1, or suggest that a drug may be a different BDDCS class at a lower dosage.

THE EXTENSIONS OF BDDCS

Food Effects (High-Fat Meals)

Fleisher et al., *Clin Pharmacokinet*. 36(3):233-254, 1999



The observed effects of high fat meals on the extent of bioavailability, F_{extent}, is consistent with high fat meals inhibiting transporters.

Even if this is not found to be true in all cases, the supposition allows predictions of food effects on drug bioavailability.

However, many factors are related to food effects, and the predictions here on F are only correct @ 70% of the time.

[Custodio et al. Adv. Drug Deliv. Rev. **60**:717-733 (2008)]

In my opinion, the 70% predictability of food effects using BDDCS is better than the reliability of food effect studies in animals.

Improving the Prediction of the Brain Disposition of Orally Administered Drugs Using BDDCS

F. Broccatelli, C.A. Larregieu, G. Cruciani, T.I. Oprea and L.Z. Benet

Advanced Drug Delivery Reviews 64: 95-109 (2012)

From the literature we were able to identify 153 drugs that met three criteria:

a) central or lack of central human pharmacodynamic effects were known

b) the drug's permeability/metabolism and BDDCS class were identified

c) information was available as to whether the drug was or was not a substrate for P-glycoprotein (since it is generally believed that P-gp substrates do not yield central effects)

In the analysis we found 17 of the 153 drugs were high permeability BDDCS Class 1 compounds that were also good substrates of P-glycoprotein in cellular systems.

But all of those 17 BDDCS Class 1 drugs exhibited central pharmacodynamic effects in humans.

Class 1 Drugs

A major proposition of BDDCS is that Class 1, P450/UGT metabolized drugs are not substrates of clinical relevance for transporters in the intestine, liver, kidney and brain.

Another Implication

Class 1 compounds will achieve brain concentrations whether this is desired or not for an NME, which could be the rationale for not always wanting Class 1 NMEs.

The Extensions of BDDCS

- Effect of Uremic Toxins on Transport and Metabolism of Different Biopharmaceutics Drug Disposition Classification Systems Xenobiotics. M Reyes & LZ Benet, J Pharm Sci 2011,100:3831-3842
- QSAR Modeling and Data Mining Link Torsades de Pointes Risk to the Interplay of Extent of Metabolism, Active Transport, and HERG Liability. F Broccatelli et al., Mol Pharmaceut 2012,9:2290-2301.
- Eco-Directed Sustainable Prescribing: Feasibility for Reducing Water Contamination by Drugs. CG Daughton, Sci Total Environ 2014,15:392-404
- Relationship Between Characteristics of Medications and Drug-Induced Liver Disease Phenotype and Outcome. R Vuppalanchi et al. Clin Gastroenterol Hepatol 2014,12:1550-1555.

The Extensions of BDDCS

- **Few Drugs Display Flip-Flop Pharmacokinetics and These Are Primarily Associated with Classes 3 and 4 of the BDDCS. KL Garrison, S Sahin & LZ Benet, J Pharm Sci 2015, 104:3229-3235**

- **Use of the Biopharmaceutics Drug Disposition Classification System (BDDCS) to Predict the Occurrence of Idiosyncratic Cutaneous Adverse Drug Reactions Associated with Antiepileptic Drug Usage. R Chan, C-y Wei, Y-t Chen & LZ Benet, AAPS J [Epub ahead of print, March 7, 2016]**

FDA ALERT [12/12/2007]: Dangerous or even fatal skin reactions (Stevens Johnson syndrome and toxic epidermal necrolysis), that can be caused by carbamazepine therapy, are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Genetic tests for HLA-B*1502 are already available. Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine. If they test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions. Patients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of these events ever developing from carbamazepine. This is true for patients of any ethnicity or genotype, including patients positive for HLA-B*1502. This new safety information will be reflected in updated product labeling.

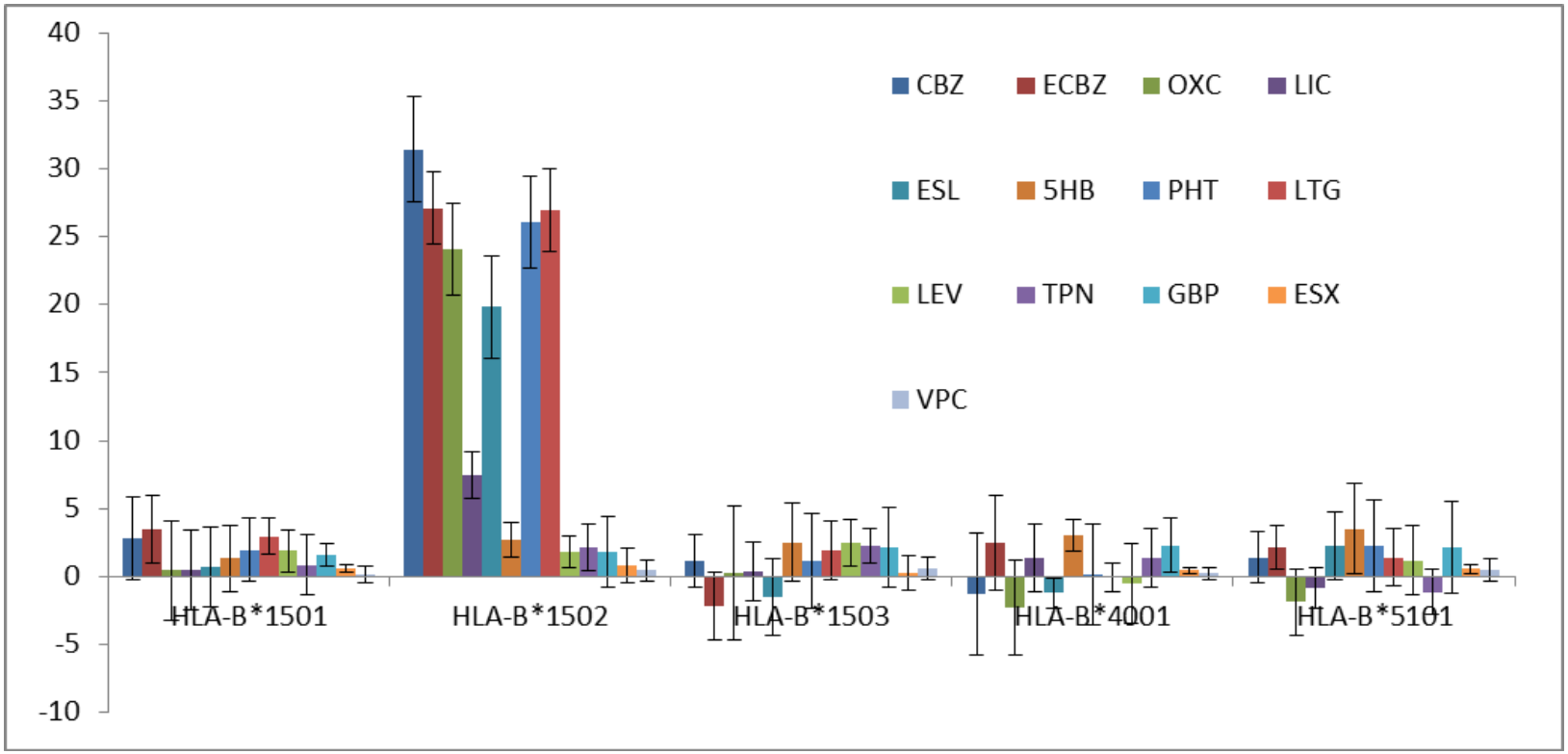
Added to the Dilantin™ (phenytoin) label September 2013 under the heading Serious Dermatologic Reactions

"Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLAB*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502.

The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied."

Added to the Lamictal™ (lamotrigene) in October 2010 and Trileptal™ (oxcarbazepine) label in June 2014 under the heading Serious Dermatologic Reactions

Surface Plasma Resonance Relative Response Measures of Specific Interactions of Anti-Epileptic Drugs to 5 HLA-B Allelic Variants for 6 BDDCS Class 2 Drugs (CBZ-carbamazepine, ECBZ-carbamazepine-10,11 epoxide, OXC-oxcarbazepine, PHT-phenytoin, ESL- eslicarbazepine and LTG-lamotrigine), 3 BDDCS Class 1 Drugs (LIC-licarbazepine, ESX-ethosuximide and VPC, valproic acid) and 4 BDDCS Class 3 Compounds (LEV-levetiracetam, TPN-topiramate, GBP-gabapentin and 5HB-5H-dibenzazepine)



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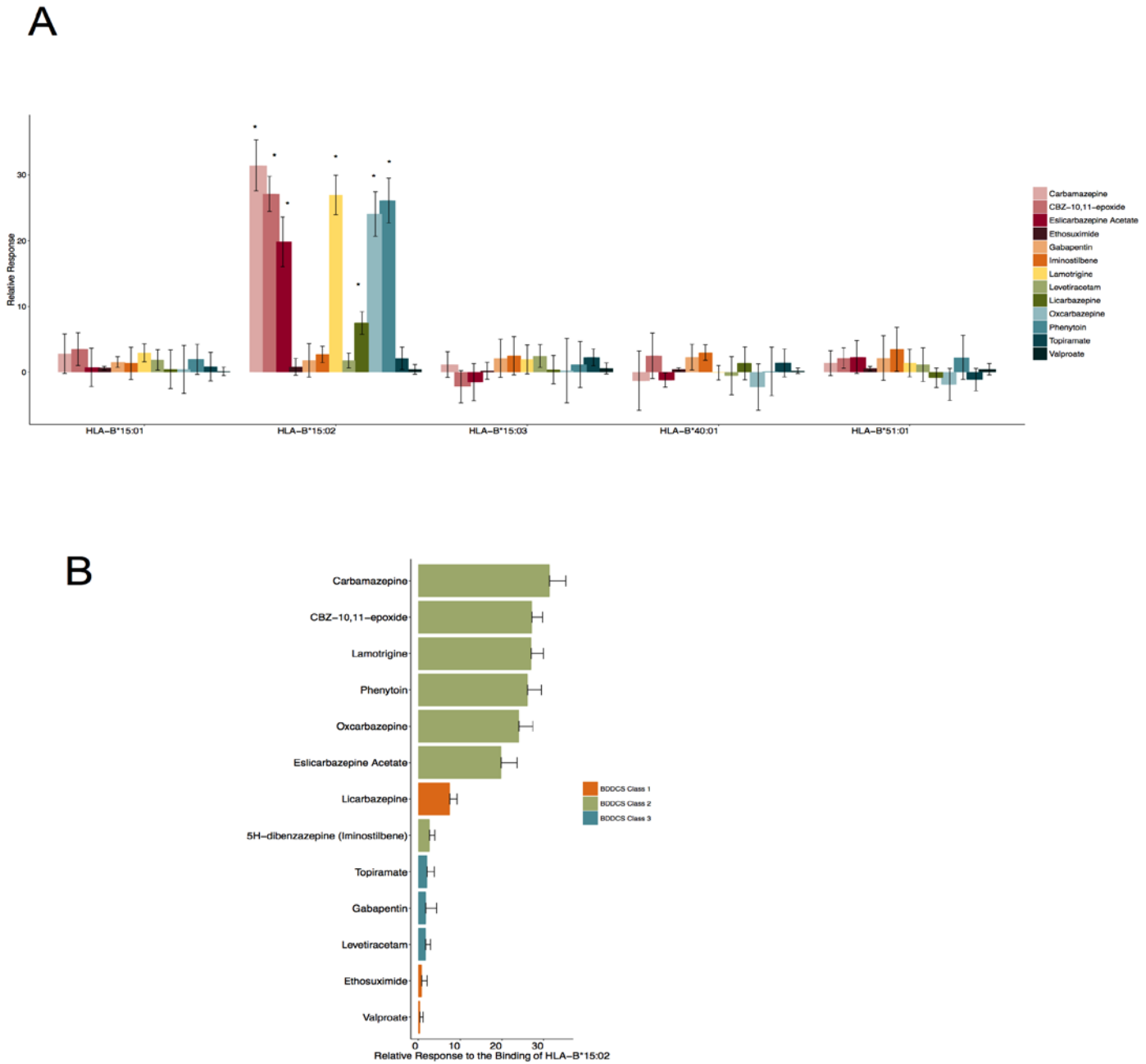
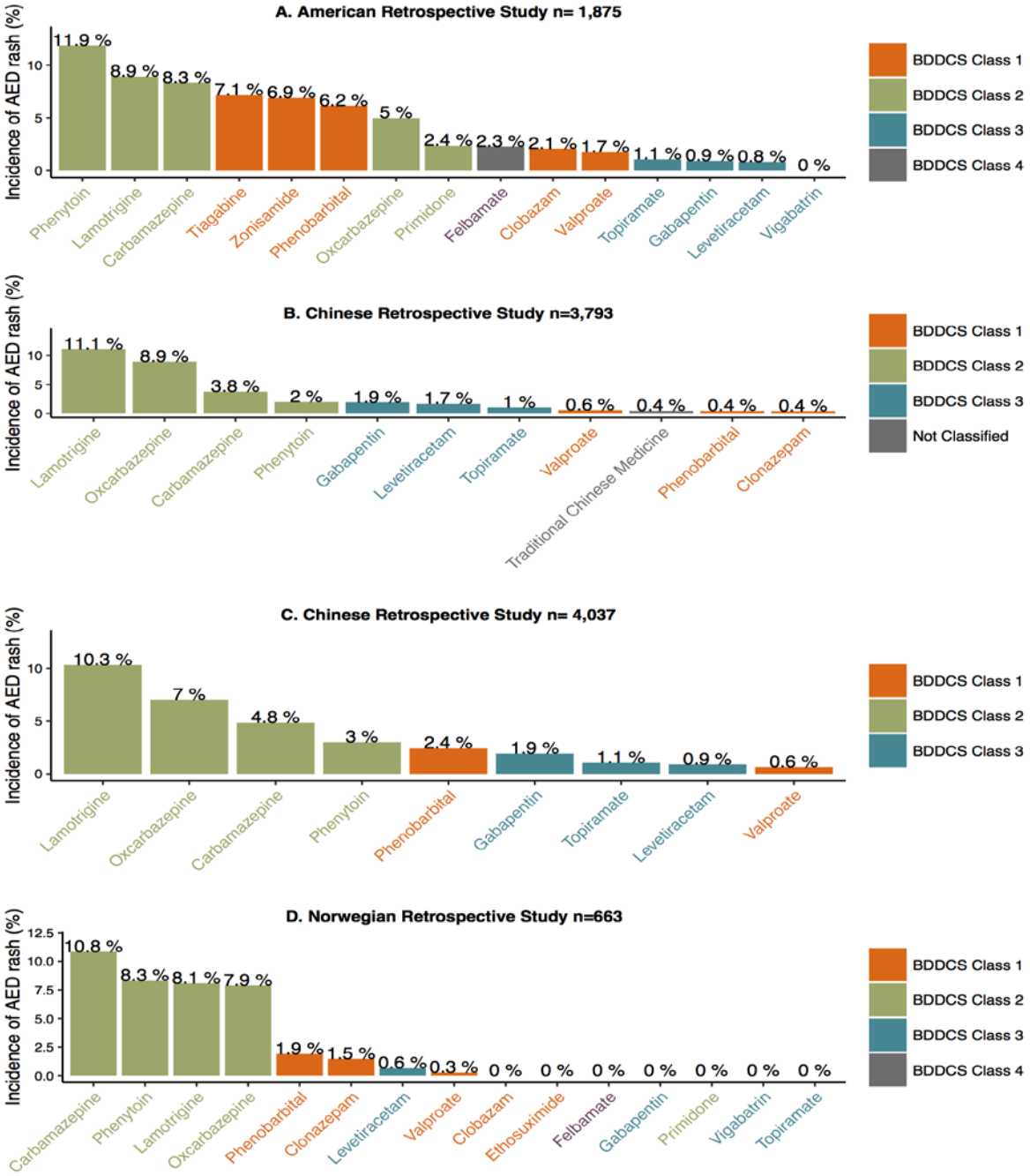


Figure 2A. Surface Plasmon Resonance (SPR) data demonstrating the specific interactions of 10 AEDs, 2 metabolites and 1 non-active structural backbone (1mM) to HLA-B*15:01, HLA-B*15:02, HLA-B*15:03, HLA-B*40:01, and HLA-B*51:01.* P<0.05 show compounds with a significant difference f



Chan et al. AAPS J [Epub ahead of print, March 7, 2016]

Conclusions

The purpose of BDDCS is to provide a qualitative predictive platform prior to any in vivo studies in animals or humans as to the potential characteristics of the NME in terms of it's disposition characteristics.

BDDCS doesn't propose that every drug in the class will be substrates or not substrates for uptake and efflux transporters. Rather, BDDCS enumerates what interactions should and should not be investigated.

It is intended that BDDCS be used in concert with more mechanism specific and quantitative approaches such as ECCS (Pfizer), CPathPred (Sugiyama) and ECCCS (Novartis).

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