Pharmacogénétique et individualisation des traitements en neuropsychiatrie

Vincent HAUFROID

Cliniques Universitaires St Luc

UCLouvain

Louvain centre for Toxicology and Applied Pharmacology (LTAP)

No conflicts of interest to declare

Pharmacogenetics in pharmacotherapy

Pharmacogenetics (PGx)

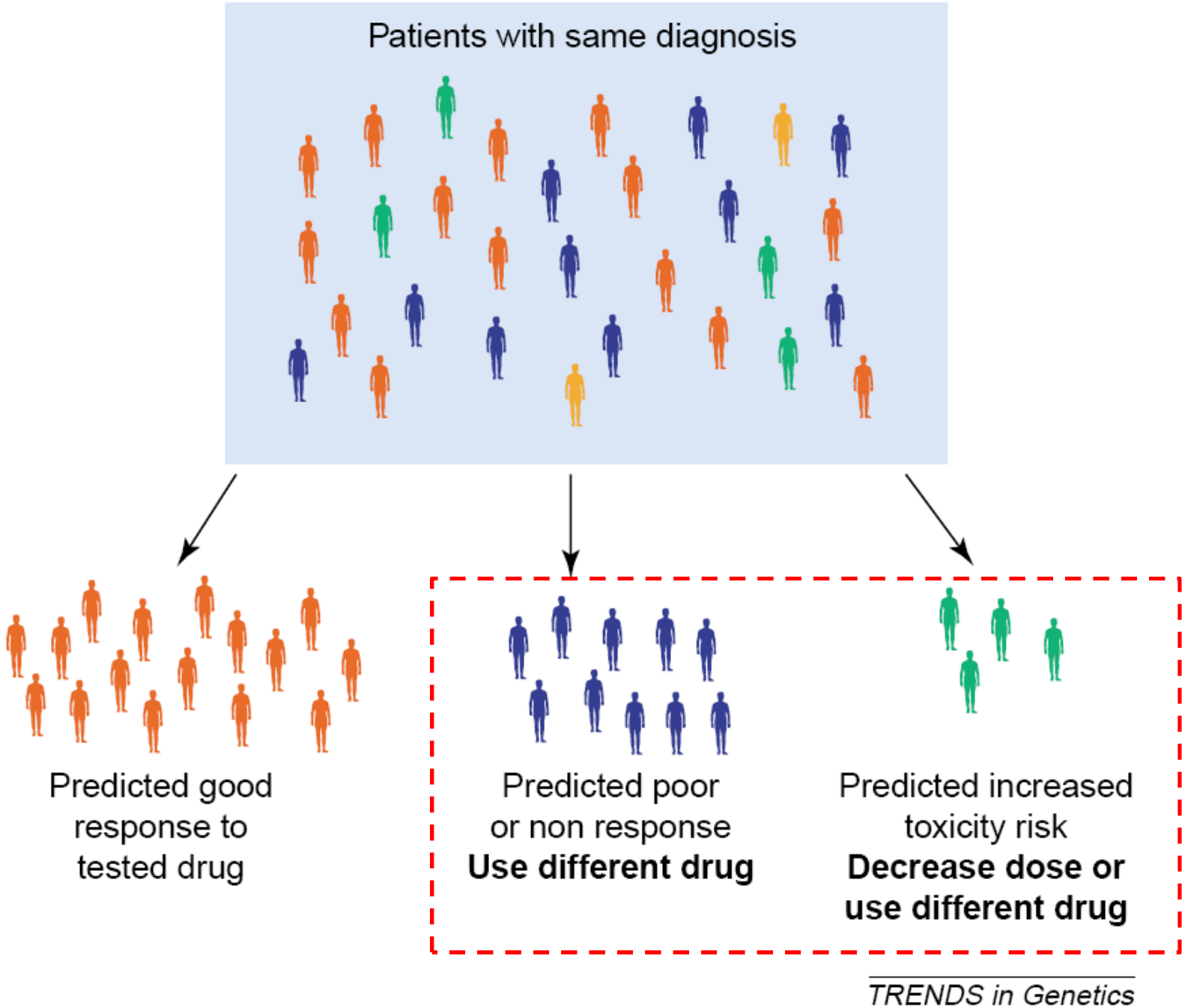
*"The study of variations in DNA sequence as related to **drug response**" (EMA and US FDA)*

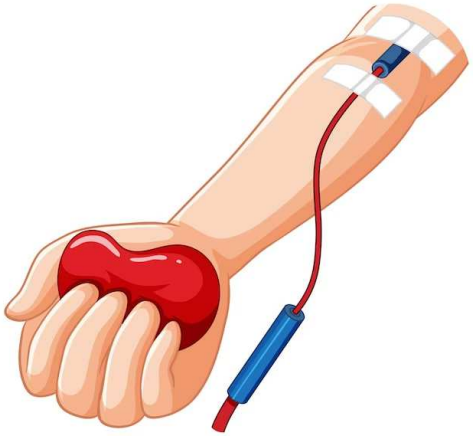
Including

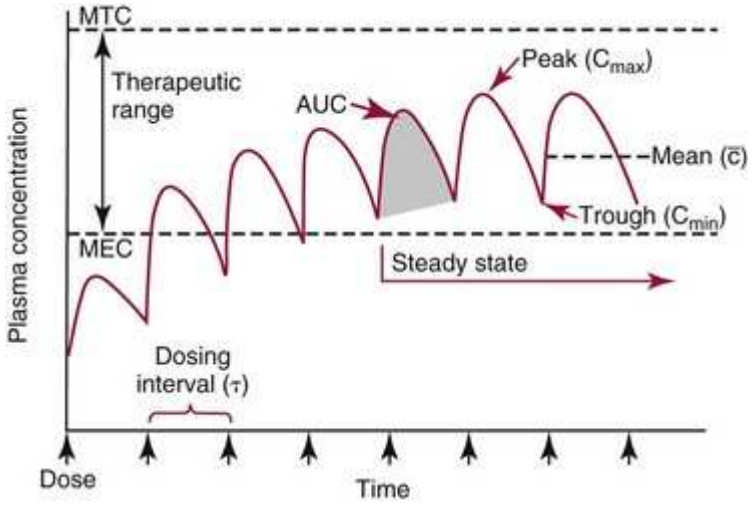
- Therapeutic efficacy
- Adverse drug reactions

"Here is my sequence…"

(The New Yorker, 2000)


Patients with same diagnosis
Predicted good response to tested drug
Predicted poor or non response
Use different drug
Predicted increased toxicity risk
Decrease dose or use different drug
TRENDS in Genetics





Review

Thieme

Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017

Authors

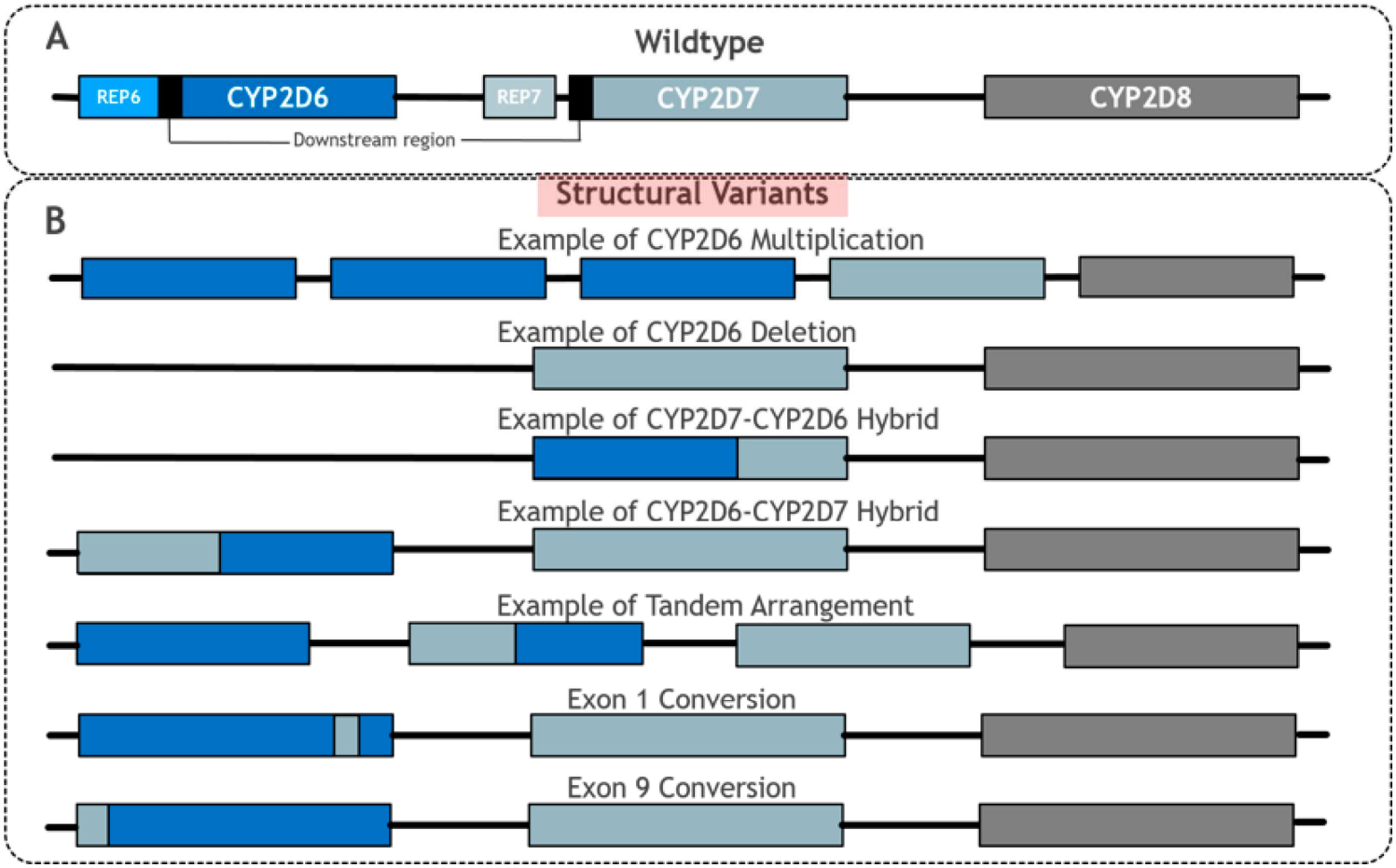
C. Hiemke[1, 2], N. Bergemann[3], H. W. Clement[4], A. Conca[5], J. Deckert[6], K. Domschke[7], G. Eckermann[8], K. Egberts[9], M. Gerlach[9], C. Greiner[10], G. Gründer[11], E. Haen[12], U. Havemann-Reinecke[13], G. Hefner[14], R. Helmer[15], G. Janssen[16], E. Jaquenoud[17], G. Laux[18], T. Messer[19], R. Mössner[20], M. J. Müller[21], M. Paulzen[11], B. Pfuhlmann[22], P. Riederer[6], A. Saria[23], B. Schoppek[24], G. Schoretsanitis[25], M. Schwarz[26], M. Silva Gracia[12], B. Stegmann[12], W. Steimer[27], J. C. Stingl[10], M. Uhr[28], S. Ulrich[29], S. Unterecker[6], R. Waschgler[30], G. Zernig[23, 31], G. Zurek[32], P. Baumann[33]

Hiemke et al. *Pharmacopsychiatry* 2018; **51**: 9-62.

Psychotropic drugs and CYPs

	1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4 3A5	Pgp
Bupropion		!							
Escitalopram									
Paroxetine									
Sertraline									
Venlafaxine						!			
Aripiprazole									
Olanzapine									
Quetiapine									
Risperidone						!		!	

CYP2D6 genetics



172 different alleles (https://www.pharmvar.org, june 2023)

Allele	SNPs to be detected	Predicted enzyme activity
*1	None	Normal (AS: 1)
*2	-1584C>G, 1661G>C, 2850C>T, 4180G>C	Normal
*3	**2549A>del**	Absent (AS: 0)
*4	100C>T, 1661G>C, **1846G>A**, 2850C>T, 4180G>C	Absent
*5	**Deletion**	Absent
*6	**1707T>del**, 4180G>C	Absent
*7	**2935A>C**	Absent
*8	1661G>C, **1758G>T**, 2850C>T, 4180G>C	Absent
*9	**2613delAGA**	Reduced (AS: 0,25)
*10	**100C>T**, 1661G>C, 4180G>C	Reduced (AS: 0,25)
*11	**883G>C**, 1661G>C, 2850C>T, 4180G>C	Absent
*15	**138insT**	Absent
*17	**1023C>T**, 1661G>C, **2850C>T**, 4180G>C	Reduced (AS: 0,5)
*29	1659G>A, 1661G>C, 2850C>T, 3183G>A, 4180G>C	Reduced (AS: 0,5)
*35	-1584C>G, 31G>A, 1661G>C, 2850C>T, 4180G>C	Normal
*41	1661G>C, 2850C>T, **2988G>A**, 4180G>C	Reduced (AS: 0,25)
*1xN, *2xN or *35xN	**Duplication**	Increased (AS: 2)

Translation of genotype into a qualitative measure of phenotype (genotype-based phenotype)

Likely phenotype	Previous CPIC activity score definition	Previous DPWG activity score definition	NEW standardized activity score definition	Examples of *CYP2D6* diplotypes for new system
Ultrarapid metabolizer (**UM**)	>2	>2,5	>2,25	**1/*1x2*
Normal metabolizer (**NM**)	1 - 2	1,5 - 2,5	1,25 - 2,25	**1/*1, *1/*2, *1/*9, *1/*41, *2/*2, *1/*10, *2x2/*10*
Intermediate metabolizer (**IM**)	0,5	0,5 - 1	0,25 - 1	**4/*10, *4/*41, *1/*5, *10/*10, *41/*41*
Poor metabolizer (**PM**)	0	0	0	**3/*4, *4/*4, *5/*5, *4/*5, *5/*6*

At the European level (> 700 million subjects)

7%
> 50 million subjects have no CYP2D6 enzymes (PMs)

- Too slow drug metabolism
- Too high drug levels at ordinary dosage
- **High risk for ADRs**
- No response from certain prodrugs (e.g. codeine)

3,5%
> 25 million subjects have *CYP2D6* gene duplications (UMs)

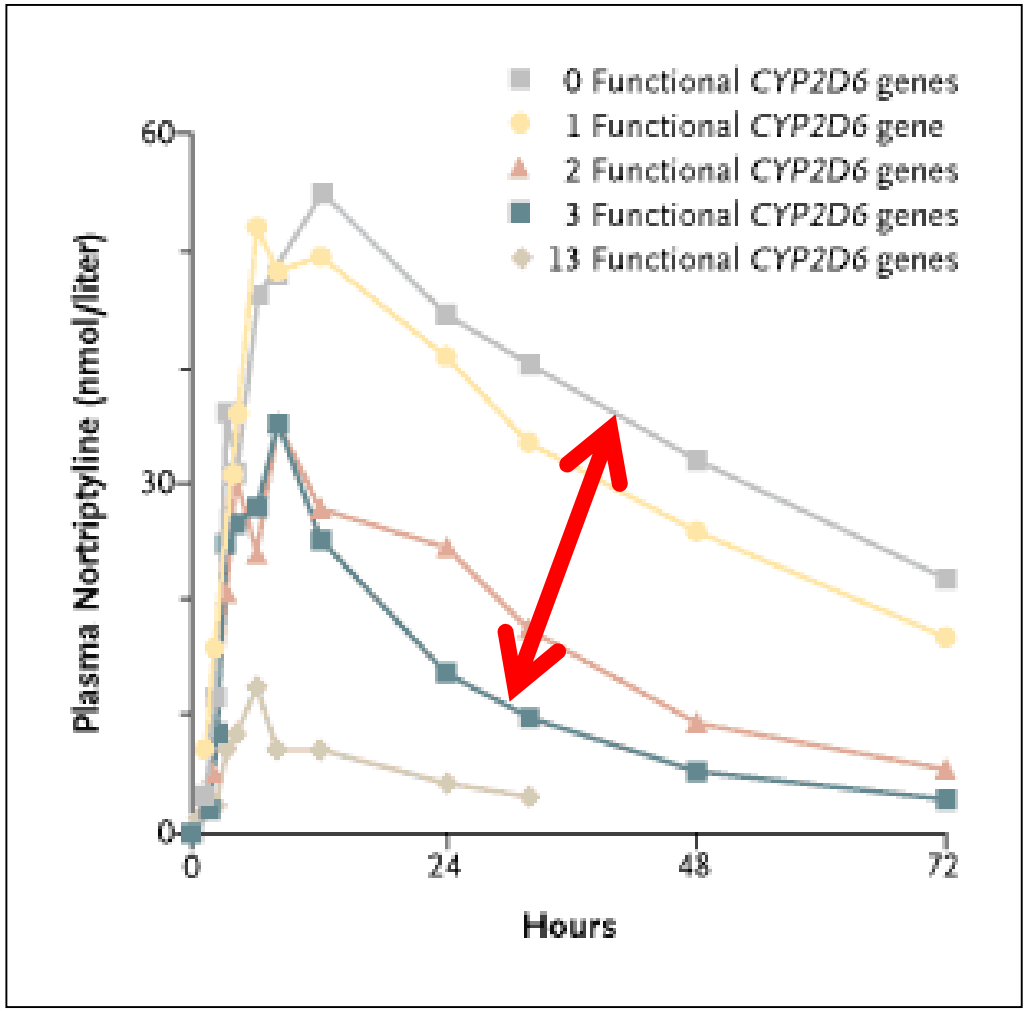
- Too rapid drug metabolism
- **No drug response** at ordinary dosage (non-responders) ≠ bad compliance !
- ADRs from certain prodrugs (e.g. codeine)

CYP2C19 genetics

Metabolizer Phenotype	CYP2C19 Enzyme Activity	Examples of Genotypes
Ultra-rapid metabolizers (**UM**)	Increased	**17/*17* ~5%
Rapid metabolizers (**RM**)	Increased	**1/*17*
Normal metabolizer (**NM**)	Normal	**1/*1*
Intermediate metabolizer (**IM**)	Reduced	**1/*2, *1/*3, *2/*17*
Poor metabolizer (**PM**)	Absent	**2/*2, *2/*3, *3/*3* ~3%

39 different alleles (https://www.pharmvar.org, june 2023)

PK impact of CYP2D6 variants has long been known…



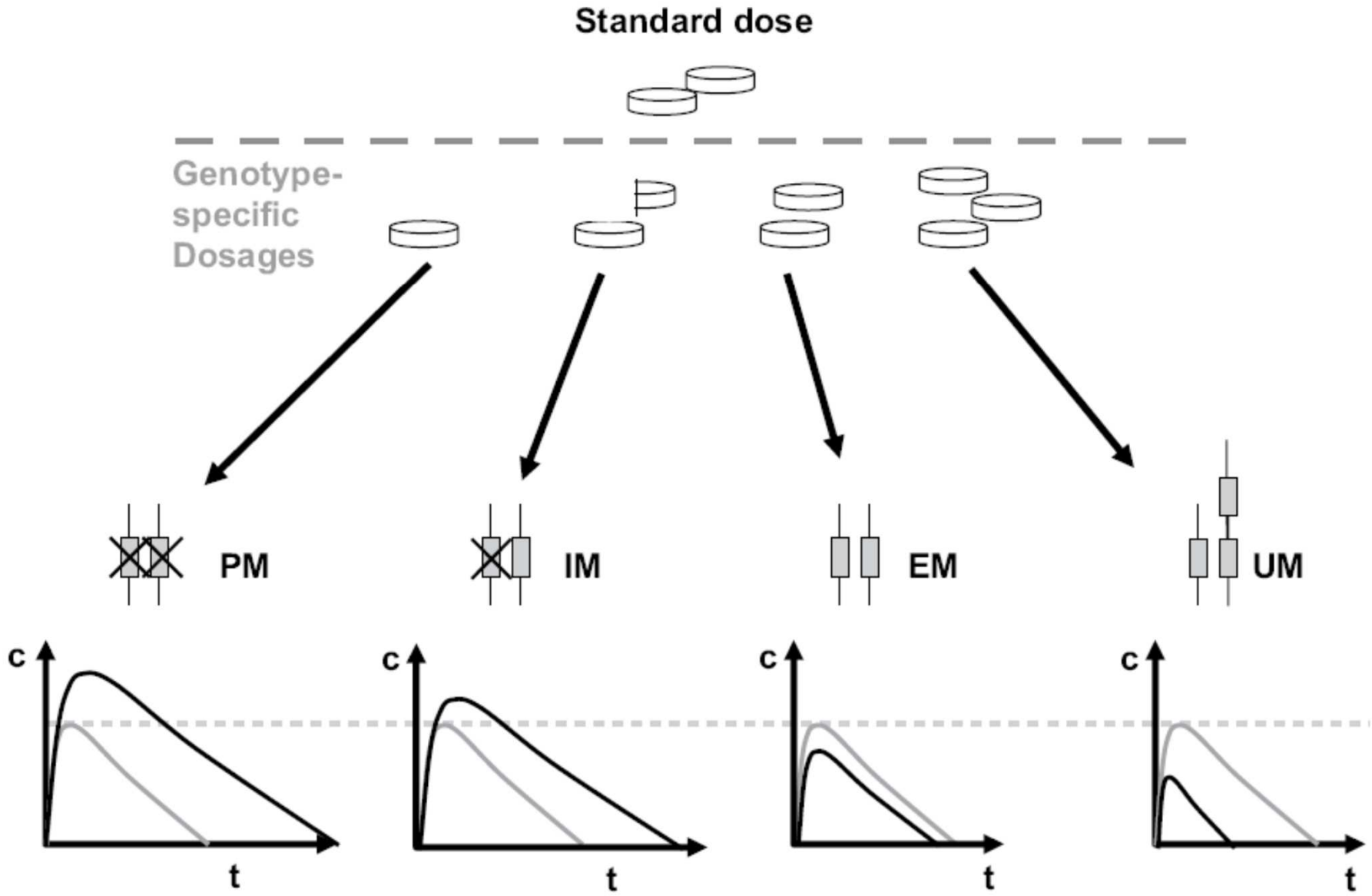
25 mg nortriptyline

<u>AUC relative:</u>

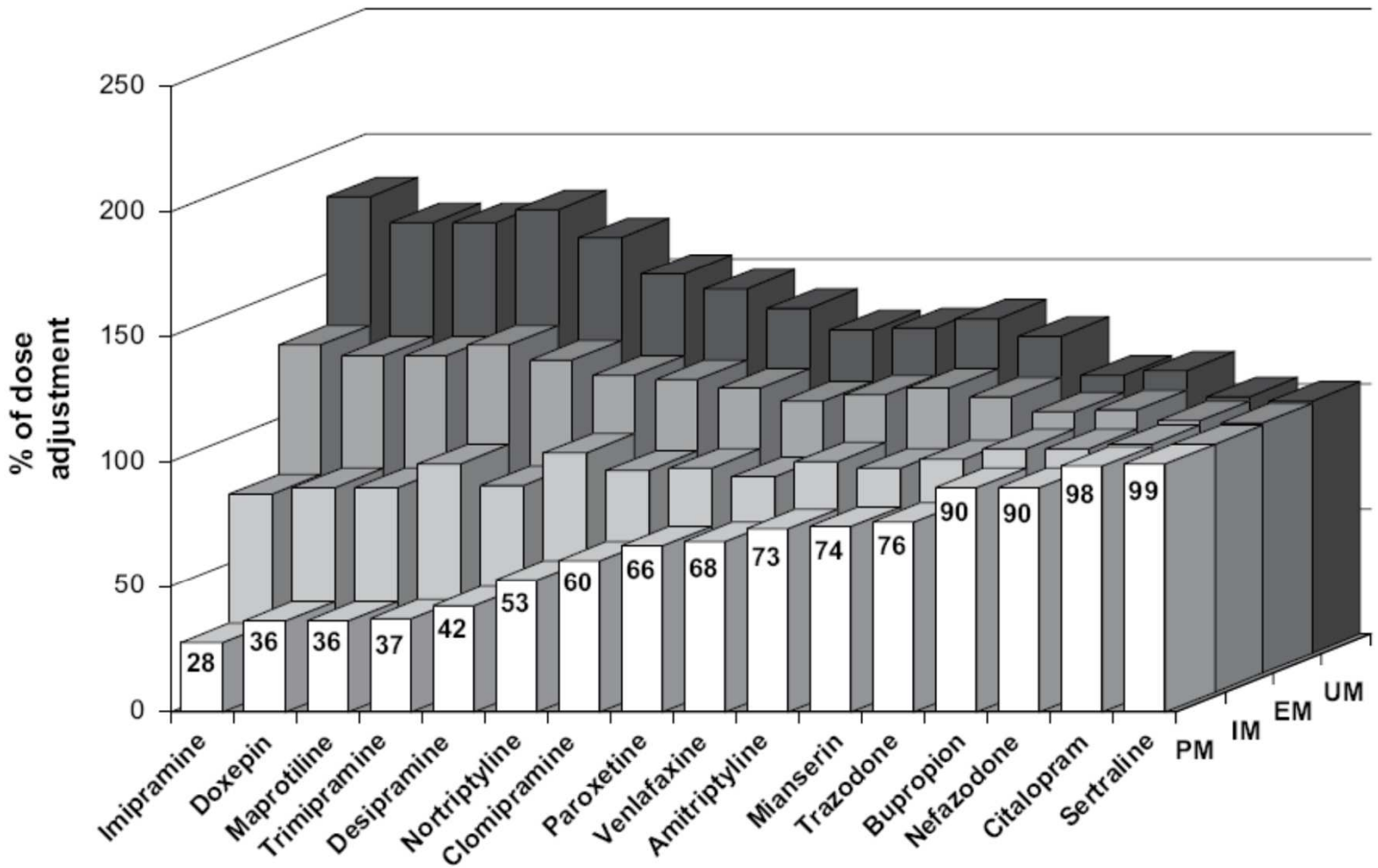
PM/UM: >5

Dalen et al. *Clin Pharmacol Ther* 1998; **63**: 444-52.

Population-based versus individualization of dosing



Preliminary (non validated) dosing adjustments

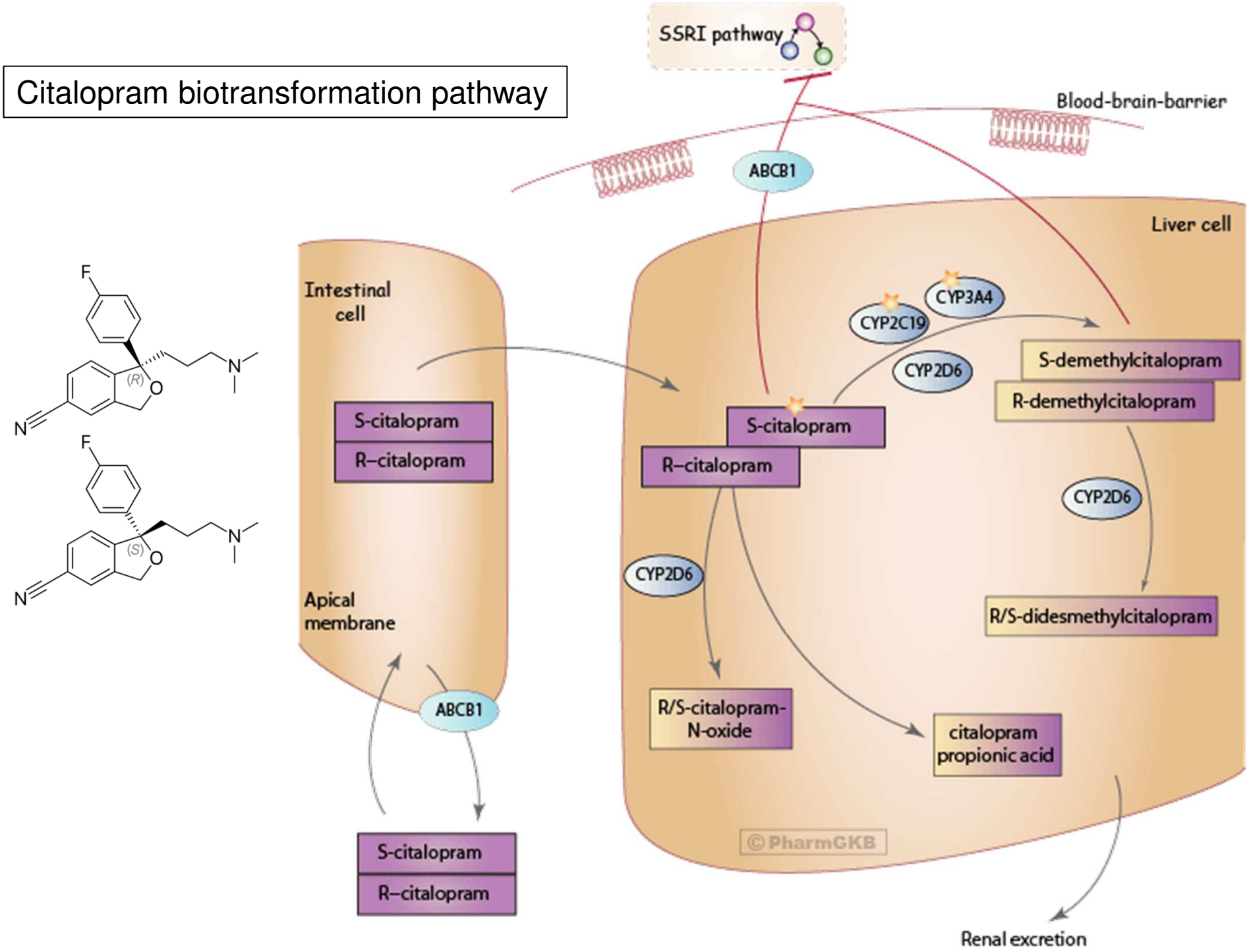


Seeringer et al. *Clin Lab Med* 2008; **28**: 619-626.

Psychotropic drugs and CYPs

	1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4 3A5	Pgp
Bupropion		!							
Escitalopram									
Paroxetine									
Sertraline									
Venlafaxine						!			
Aripiprazole									
Olanzapine									
Quetiapine									
Risperidone						!		!	

Citalopram biotransformation pathway



Impact of *CYP2C19* Genotype on Escitalopram Exposure and Therapeutic Failure: A Retrospective Study Based on 2,087 Patients

Marin M. Jukić, Ph.D., Tore Haslemo, Ph.D., Espen Molden, Ph.D., Magnus Ingelman-Sundberg, Ph.D.

Objective: The antidepressant escitalopram is predominantly metabolized by the polymorphic CYP2C19 enzyme. The authors investigated the effect of *CYP2C19* genotype on exposure and therapeutic failure of escitalopram in a large patient population.

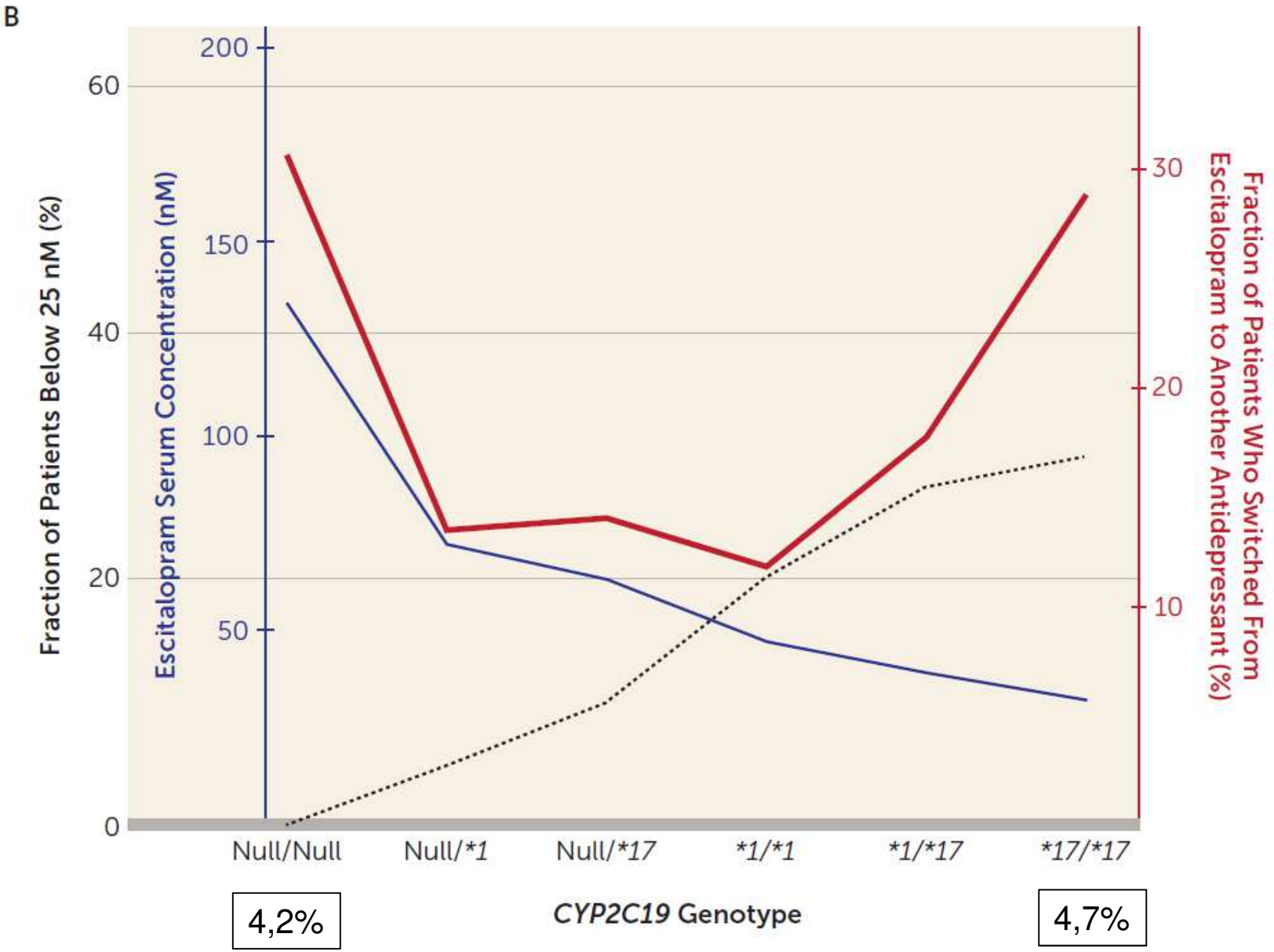
Method: A total of 4,228 escitalopram serum concentration measurements from 2,087 *CYP2C19*-genotyped patients 10–30 hours after drug intake were collected retrospectively from the drug monitoring database at Diakonhjemmet Hospital in Oslo. The patients were divided into subgroups based on *CYP2C19* genotype: those carrying inactive (*CYP2C19*Null) and gain-of-function (*CYP2C19*17*) variant alleles. The between-subgroup differences in escitalopram exposure (endpoint: dose-harmonized serum concentration) and therapeutic failure (endpoint: switching to another antidepressant within 1 year after the last escitalopram measurement) were evaluated by multivariate mixed model and chi-square analysis, respectively.

Results: Compared with the *CYP2C19*1/*1* group, escitalopram serum concentrations were significantly increased 3.3-fold in the *CYP2C19*Null/Null group, 1.6-fold in the *CYP2C19**Null/**1* group, and 1.4-fold in the *CYP2C19*Null/**17* group, whereas escitalopram serum concentrations were significantly decreased by 10% in the *CYP2C19*1/*17* group and 20% in the *CYP1C19*17/*17* group. In comparison to the *CYP2C19*1/*1* group, switches from escitalopram to another antidepressant within 1 year were 3.3, 1.6, and 3.0 times more frequent among the *CYP2C19*Null/Null, *CYP2C19*1/*17*, and *CYP1C19*17/*17* groups, respectively.

Conclusions: The *CYP2C19* genotype had a substantial impact on exposure and therapeutic failure of escitalopram, as measured by switching of antidepressant therapy. The results support the potential clinical utility of *CYP2C19* genotyping for individualization of escitalopram therapy.

AJP in Advance (doi: 10.1176/appi.ajp.2017.17050550)

Jukic et al. *Am J Psychiat* 2018; **175**: 463-70.



Jukic et al. *Am J Psychiat* 2018; **175**: 463-70.

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6*, *CYP2C19*, *CYP2B6*, *SLC6A4*, and *HTR2A* Genotypes and Serotonin Reuptake Inhibitor Antidepressants

Chad A. Bousman[1,2,3,4,5,6,†], James M. Stevenson[7,8,†], Laura B. Ramsey[9,10,11], Katrin Sangkuhl[12], J. Kevin Hicks[13], Jeffrey R. Strawn[11,14,15], Ajeet B. Singh[16], Gualberto Ruaño[17,18], Daniel J. Mueller[19,20], Evangelia Eirini Tsermpini[21], Jacob T. Brown[22], Gillian C. Bell[23], J. Steven Leeder[24,25], Andrea Gaedigk[24,25], Stuart A. Scott[26,27], Teri E. Klein[12], Kelly E. Caudle[28] and Jeffrey R. Bishop[29,30,*]

Guidelines for 7 drugs

- paroxetine, fluvoxamine, venlafaxine, vortioxetine and **CYP2D6**
- citalopram, escitalopram, sertraline and **CYP2C19**
- sertraline and **CYP2B6**

Absence of consensus for **SLC6A4** and **HTR2A**

Bousman et al. *Clin Pharmacol Ther* 2023; online ahead of print.

Summary of the recommendations (PharmGKB.org)

	PM	IM	NM	RM	UM
* Paroxetine	**50%** dose ↓	Opt.: dose ↓ 25%?	Standard dose	NA	Alternative drug
Fluvoxamine	**25-50%** dose ↓	Recommended starting dose	Standard dose	NA	--- (few data)
Venlafaxine	Alternative drug	--- (low evidence)	Standard dose	NA	--- (low evidence)
Vortioxetine	**50%** dose ↓ or alternative drug	Standard dose	Standard dose	NA	Alternative drug (or 50% dose ↑)
** Citalopram	Alternative drug or **50%** dose ↓	Standard dose or titrate TDM	Standard dose	Standard dose or titrate TDM	Alternative drug, or titrate TDM
Escitalopram	Alternative drug or **50%** dose ↓	Standard dose or titrate TDM	Standard dose	Standard dose or titrate TDM	Alternative drug, or titrate TDM
Sertraline	**50%** dose ↓ or alternative drug	Standard dose or titrate TDM	Standard dose	Standard dose	Standard dose
*** Sertraline	**25%** dose ↓ or alternative drug	Standard dose or titrate TDM	Standard dose	Standard dose	Standard dose

* CYP2D6, ** CYP2C19, and *** CYP2B6-genotype based dosing guidelines

Case report

61 year-old woman
Depression

R/ Paroxetine 20 mg/day (SE +++)

R/ Venlafaxine up to 300 mg/day
Absence of response

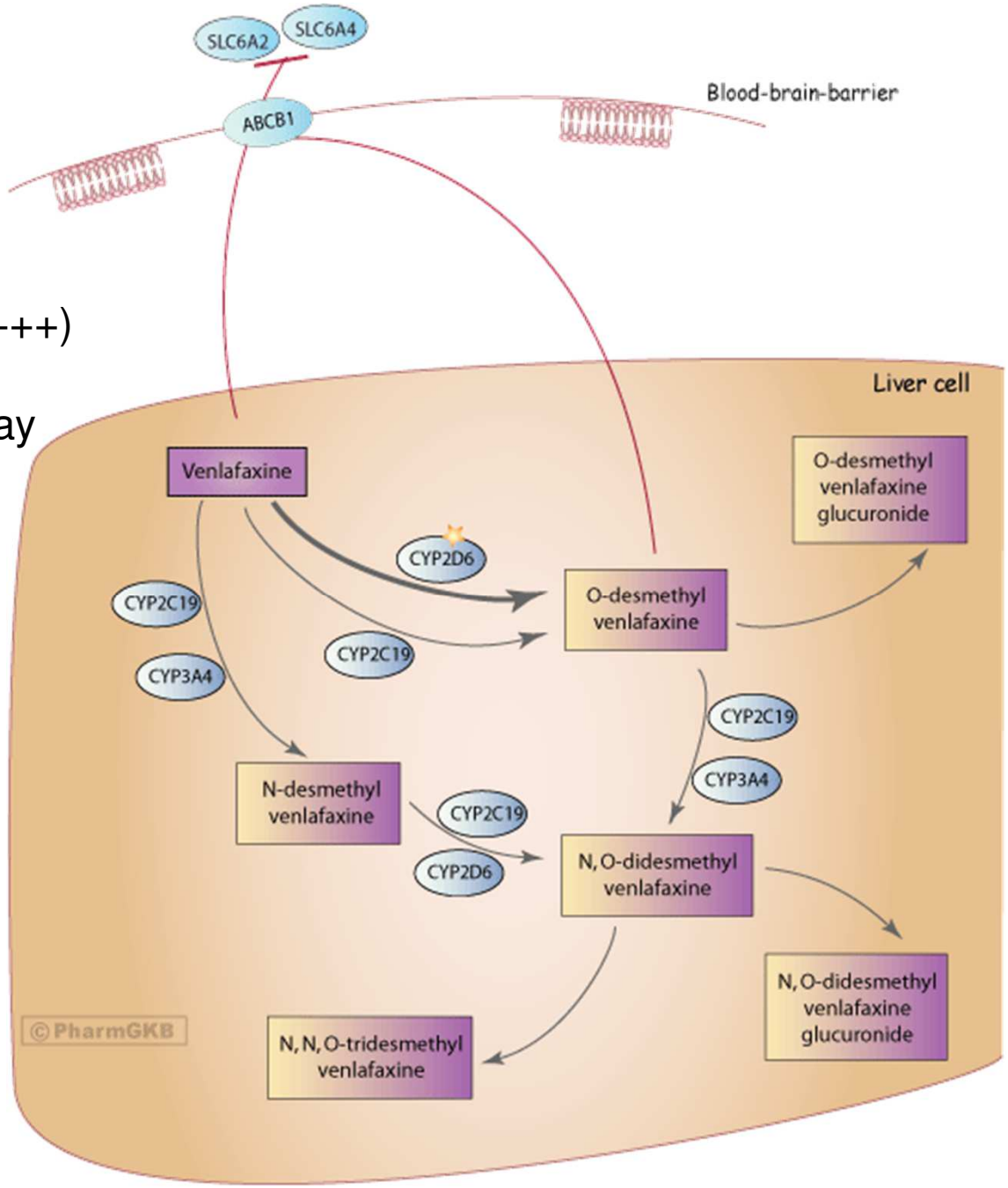
<u>TDM results</u>:

VEN: 561 ng/ml
ODV: 270 ng/ml
(Nl: sum: 100-400 ng/ml)

ODV/VEN ratio: **0,48**
(Nl: 2,70-7,70)

<u>PGx</u>:

CYP2D6*4/*4 PM
CYP2C19*1/*17 RM



Psychotropic drugs and CYPs

	1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4 3A5	Pgp
Bupropion		!							
Escitalopram									
Paroxetine									
Sertraline									
Venlafaxine						!			
Aripiprazole									
Olanzapine									
Quetiapine									
Risperidone						!		!	

Effect of *CYP2D6* genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study

Marin M Jukic, Robert L Smith, Tore Haslemo, Espen Molden, Magnus Ingelman-Sundberg**

Lancet Psychiatry 2019; 6: 418–26

Published Online April 15, 2019

Summary

Background The polymorphic CYP2D6 enzyme metabolises the antipsychotic drugs risperidone and aripiprazole to their active metabolites, 9OH-risperidone and dehydroaripiprazole. The aim of this study was to quantify the effect of *CYP2D6* genetic variability on risperidone and aripiprazole exposure and treatment in a large patient population.

1288 risperidone-treated patients

1334 aripiprazole-treated patients

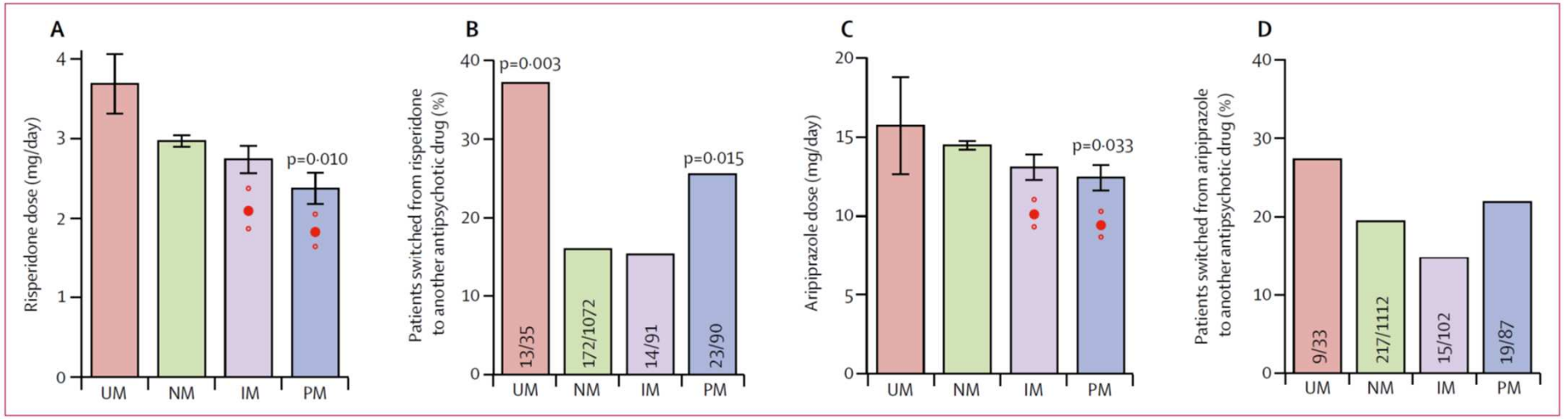


***Figure 2*: Effect of CYP2D6 metaboliser status on risperidone and aripiprazole dose and treatment failure rates**

In **A** and **C**, the dose reductions needed to compensate for the increase of risperidone exposure in patients who were intermediate metabolisers (IM) and poor metabolisers (PM; 95% CI) are indicated by red dots. Data are mean (SE). NM is the reference subgroup in all graphs. UM=ultrarapid metabolisers. NM=normal metabolisers.

Jukic et al. *Lancet Psychiatry* 2019

ARTICLE

Check for updates

Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between *CYP2D6*, *CYP3A4* and *CYP1A2* and antipsychotics

Lianne Beunk[1], Marga Nijenhuis[2]✉, Bianca Soree[2], Nienke J. de Boer-Veger[3], Anne-Marie Buunk[4], Henk Jan Guchelaar[5], Elisa J. F. Houwink[6,7], Arne Risselada[8], Gerard A. P. J. M. Rongen[9,10], Ron H. N. van Schaik[11], Jesse J. Swen[5], Daan Touw[12,13], Roos van Westrhenen[14,15,16], Vera H. M. Deneer[17,18] and Jan van der Weide[1]

The Dutch Pharmacogenetics Working Group (DPWG) aims to facilitate pharmacogenetics implementation in clinical practice by developing evidence-based guidelines to optimize pharmacotherapy. A guideline describing the gene-drug interaction between the genes *CYP2D6*, *CYP3A4* and *CYP1A2* and antipsychotics is presented here. The DPWG identified gene-drug interactions that require therapy adjustments when respective genotype is known for *CYP2D6* with aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol, and for *CYP3A4* with quetiapine. Evidence-based dose recommendations were obtained based on a systematic review of published literature. Reduction of the normal dose is recommended for aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol for *CYP2D6*-predicted PMs, and for pimozide and zuclopenthixol also for *CYP2D6* IMs. For *CYP2D6* UMs, a dose increase or an alternative drug is recommended for haloperidol and an alternative drug or titration of the dose for risperidone. In addition, in case of no or limited clinical effect, a dose increase is recommended for zuclopenthixol for *CYP2D6* UMs. Even though evidence is limited, the DPWG recommends choosing an alternative drug to treat symptoms of depression or a dose reduction for other indications for quetiapine and *CYP3A4* PMs. No therapy adjustments are recommended for the other *CYP2D6* and *CYP3A4* predicted phenotypes. In addition, no action is required for the gene-drug combinations *CYP2D6* and clozapine, flupentixol, olanzapine or quetiapine and also not for *CYP1A2* and clozapine or olanzapine. For identified gene-drug interactions requiring therapy adjustments, genotyping of *CYP2D6* or *CYP3A4* prior to treatment should not be considered for all patients, but on an individual patient basis only.

European Journal of Human Genetics; https://doi.org/10.1038/s41431-023-01347-3

Beunk et al. *Eur J Hum Genet* 2023; online ahead of print.

Table 2. Summary of the therapeutic recommendations based on *CYP2D6* and *CYP3A4* phenotype for antipsychotics.

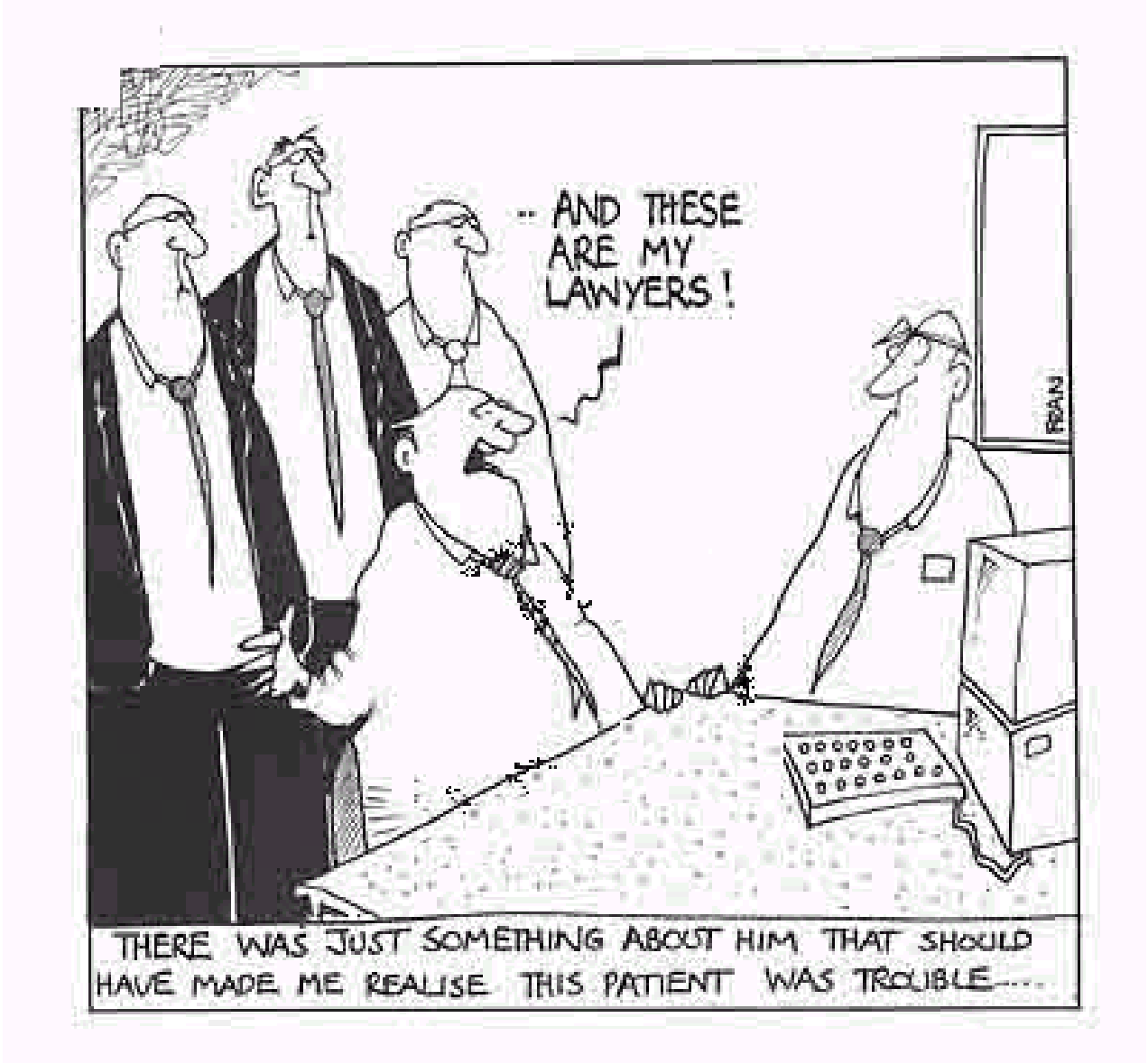
Drug	Gene	Phenotype	Therapeutic recommendation[a] (if present)[b]
Aripiprazole	*CYP2D6*	PM	Administer no more than 10 mg/day or 300 mg/month (68-75% of the normal maximum dose of aripiprazole).
Brexpiprazole	*CYP2D6*	PM	Use half of the normal dose.
Haloperidol	*CYP2D6*	PM	Use 60% of the normal dose.
	CYP2D6	UM	Use 1.5 times the normal dose or choose an alternative. Antipsychotics that are not metabolized by CYP2D6 - or to a much lesser extent - include, for example, flupentixol, penfluridol, quetiapine, olanzapine or clozapine.
Pimozide	*CYP2D6*	PM	Use no more than the following doses (50% of the normal maximum dose): - 12 years and older: 10 mg/day - younger than 12 years: 0.05 mg/kg per day to a maximum of 2 mg/day.
	CYP2D6	IM	Use no more than the following doses (80% of the normal maximum dose): - 12 years and older: 16 mg/day - younger than 12 years: 0.08 mg/kg per day to a maximum of 3 mg/day.
Risperidone	*CYP2D6*	PM	- Use 67% of the normal dose. - If problematic side effects originating in the central nervous system occur despite this reduced dose, then reduce the dose further to 50% of the normal dose.
	CYP2D6	UM	Choose an alternative or titrate the dose according to the maximum dose for the active metabolite (paliperidone) (oral 12 mg/day for adults and children from 15 years of age weighing at least 51 kg and 6 mg/day for children from 15 years of age weighing less than 51 kg; intramuscular 75 mg per 2 weeks).
Zuclopenthixol	*CYP2D6*	PM	Use 50% of the normal dose.
	CYP2D6	IM	Use 75% of the normal dose.
	CYP2D6	UM	There is insufficient information available to make a dose recommendation. If the effectiveness is insufficient: try a dose increase. Do not exceed 1.5 times the normal dose.
Quetiapine	*CYP3A4*	PM	- Indication depression: Choose an alternative. Aripiprazole appears to be less dependent on CYP3A4 for metabolism. Olanzapine is not metabolized by CYP3A4. - Other indications: Use 30% of the normal dose.

IM intermediate metaboliser, *PM* poor metaboliser, *UM* ultra-rapid metaboliser.

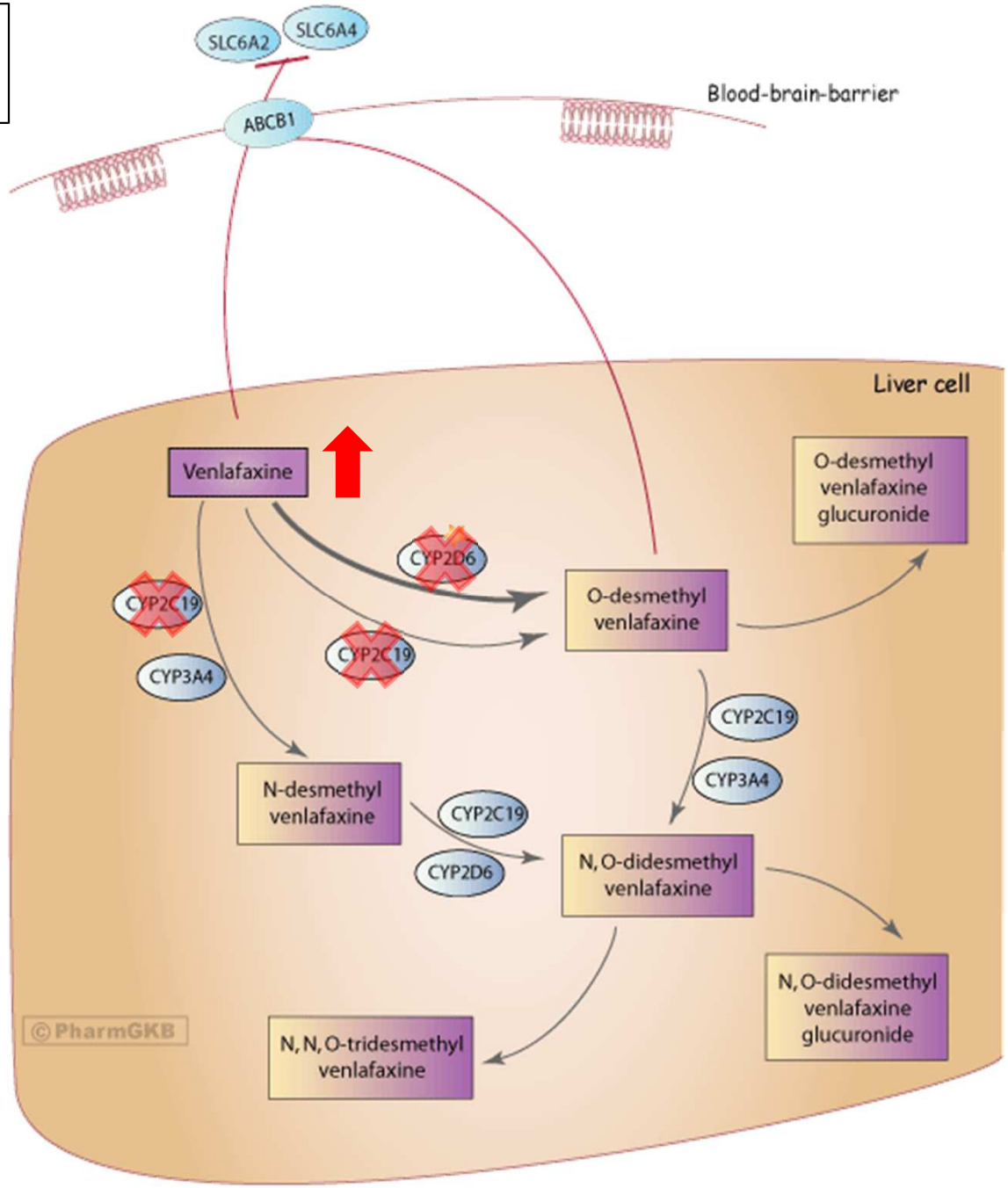
[a]In the pharmacotherapeutic recommendations, the normal dose is defined as the dose that would be given to the same patient if he or she had no gene variant.

[b]No pharmacotherapeutic recommendation: therapy adjustment is not required or beneficial for this phenotype-drug combinations. This is also true for all genotype groups/phenotypes for the following gene-drug combinations: *CYP2D6*-clozapine, *CYP2D6*-flupentixol, *CYP2D6*-olanzapine, *CYP2D6*-quetiapine, *CYP1A2*-clozapine, and *CYP1A2*-olanzapine.

Ready for pre-emptive genotyping and DNA passport ?



Venlafaxine biotransformation pathway



Forensic Science International 226 (2013) e26–e31

Contents lists available at SciVerse ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

Case report

A poor metabolizer of both CYP2C19 and CYP2D6 identified by mechanistic pharmacokinetic simulation in a fatal drug poisoning case involving venlafaxine

J. Jornil [a,*], T.S. Nielsen [a], I. Rosendal [a], J. Ahlner [b], A.L. Zackrisson [b], L.W.T. Boel [a], B. Brock [a,c]

[a] Aarhus University, Department of Forensic Medicine, Section for Forensic Pathology and Clinical Forensic Medicine & Section for Toxicology and Drug Analysis, Brendstrupgaardsvej 100, 8200 Aarhus N, Denmark

[b] Department of Forensic Genetics and Forensic Toxicology, National Board of Forensic Medicine, Artillerigatan 12, SE-587 58, Linköping, Sweden

[c] Aarhus University Hospital, Department of Clinical Biochemistry, Brendstrupgaardsvej 100, 8200 Aarhus N, Denmark

34 year old Caucasian male found death at home

Medications:

VEN 150 mg twice daily + oxycodone and ethanol

Biological results:

Blood VEN: 4,5 mg/Kg (ODV/VEN ratio 0,006 !!: Nl: 2,7-7,7)

Patient genotype:

CYP2D6*4/*5 **PM**

CYP2C19*2/*2 **PM**

Expected frequency in Caucasians: 0,07 * 0,03 = **0,21%**

UCLouvain

Cliniques universitaires SAINT-LUC UCL BRUXELLES

Un hôpital pour la Vie

Collaborators:

Pr Y. Sznajer
Pr A. De Leener
Pr N. Revencu
Phn Biol L. Boland
Dr M. Philippeau
Dr I. Derclaye
Dr L. Zahed
Dr C. Barbée
Mme S. Lachhab
Mr A. Boesmans
Mr P. Moureau
And technicians from CUSL