An International Perspective on Pharmacogenetics:
The intersections between innovation, regulation and health delivery

The Istituto Superiore di Sanita
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Session I:

New Paradigms in Biomedical Research and Drug Discovery

OECD OCDE

Enhancing the benefit to risk ratio of new pharmaceuticals with pharmacogenetic approaches: Using genomic biomarkers to influence efficacy or safety

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Drug withdrawals over last 15 years

34 drugs withdrawn from 1990 – 2004

-	13	Hepatotoxicity
-	9	QT prolongation and TdP or proarrhythmias
-	2	Drug interactions → Non-QT consequences
-	3	Other cardiac safety (valvulopathy, MI)
-	2	CNS
-	5	Other causes

What is the problem?
What is going wrong?
What can we learn?

Improving risk and benefit through pharmacogenetics

Managing pharmacokinetic variability

and

Managing pharmacodynamic variability

by pharmacogenetic biomarkers

Theranostics and Pharmacogenetics in improving safety and efficacy and drug development

- Promise
- Potential
- Pitfalls

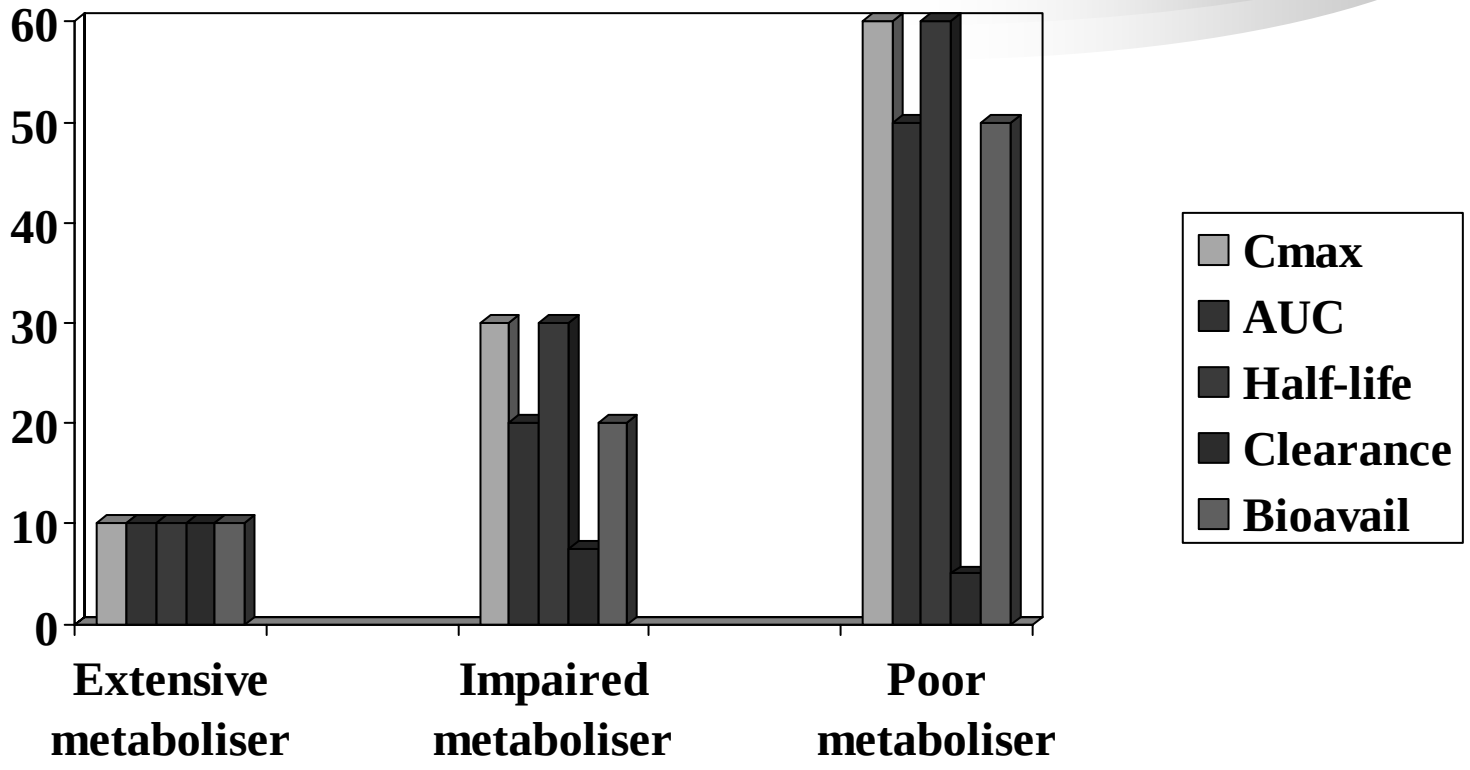
Drug metabolism by CYP P_{450} isoforms

- 315 drugs profiled for their metabolism
- Of these, 56% primarily metabolised by CYP P_{450} isoforms
  - 50% CYP 3A4 *(about 30% of liv*
  - 20% **CYP 2D6 *** *(about 2% of liv* *nt)*
  - 15% CYP 2C9/19 *, CYP 2C8 * *(about 20% of liver P450 content)*
  - 15% CYPs 2E1, 2A6 *, 2B6 *, 1A2 * etc *(about 24% of liver P450 content)*

CYP2D6 is the most widely studied

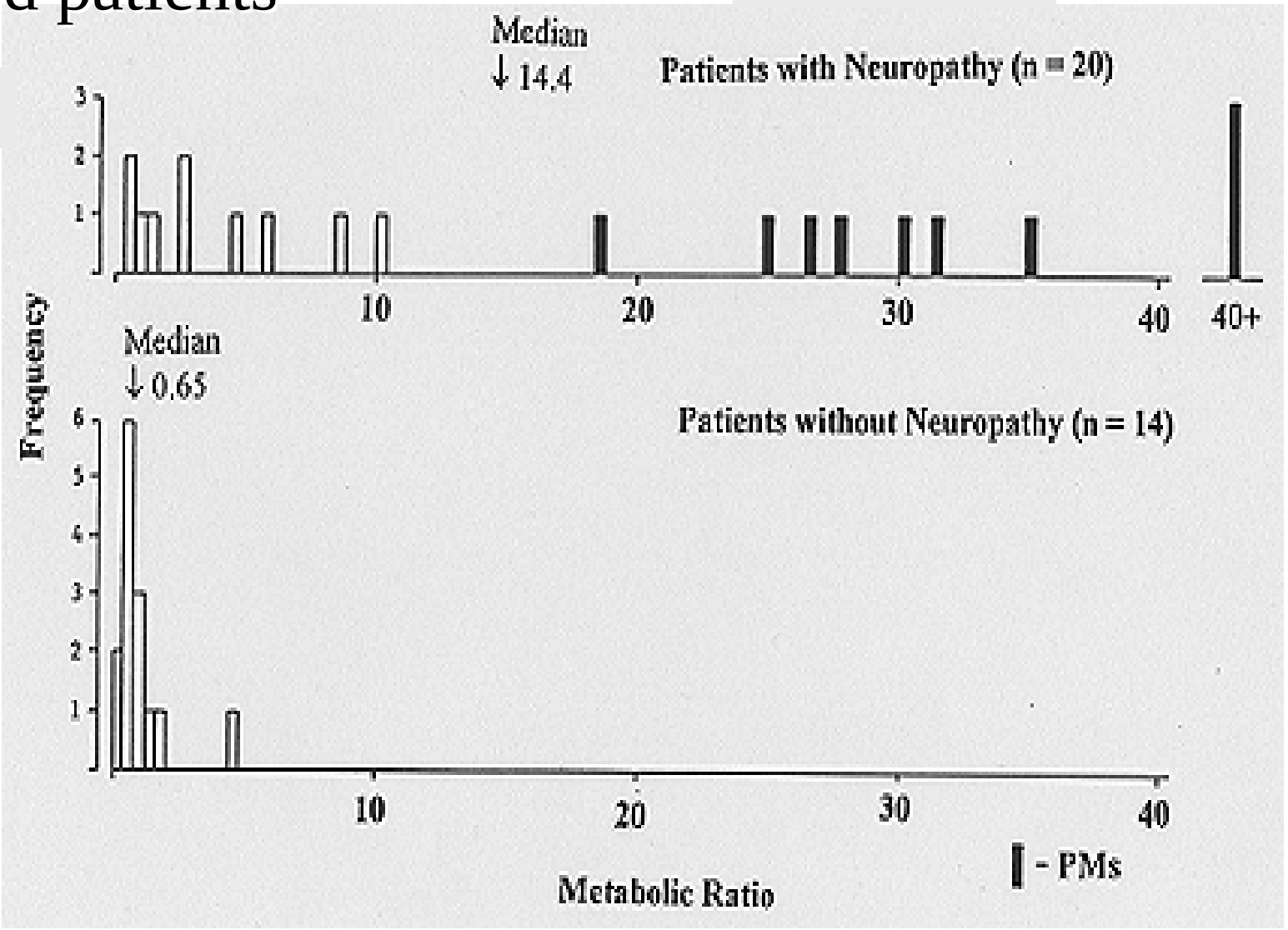
* These CYP isoforms display genetic polymorphism

Pharmacokinetic Consequences of CYP 2D6 Polymorphism



Extensive metaboliser arbitrarily assigned 10 units

Debrisoquine metabolic ratios in perhexiline-treated patients

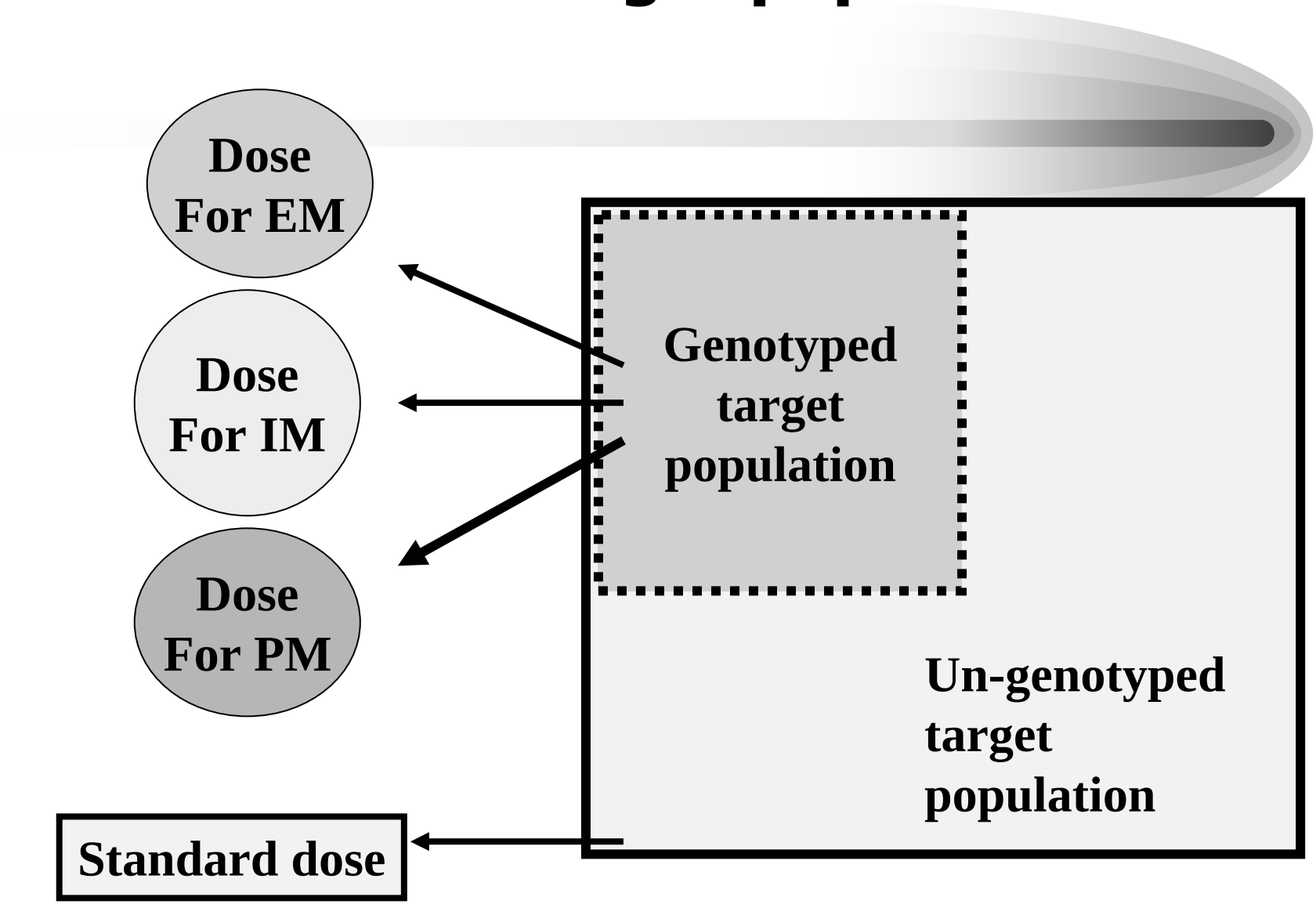


Shah RR et al, Br Med J, 1982; 284: 295-299

Safe and effective dose schedules

	Nortriptyline	Perhexiline
Ultrarapid EMs	> 500 mg	300-500 mg
EMs	100-150 mg	100-250mg
PMs	20-30 mg	10-25 mg

Indication and target population



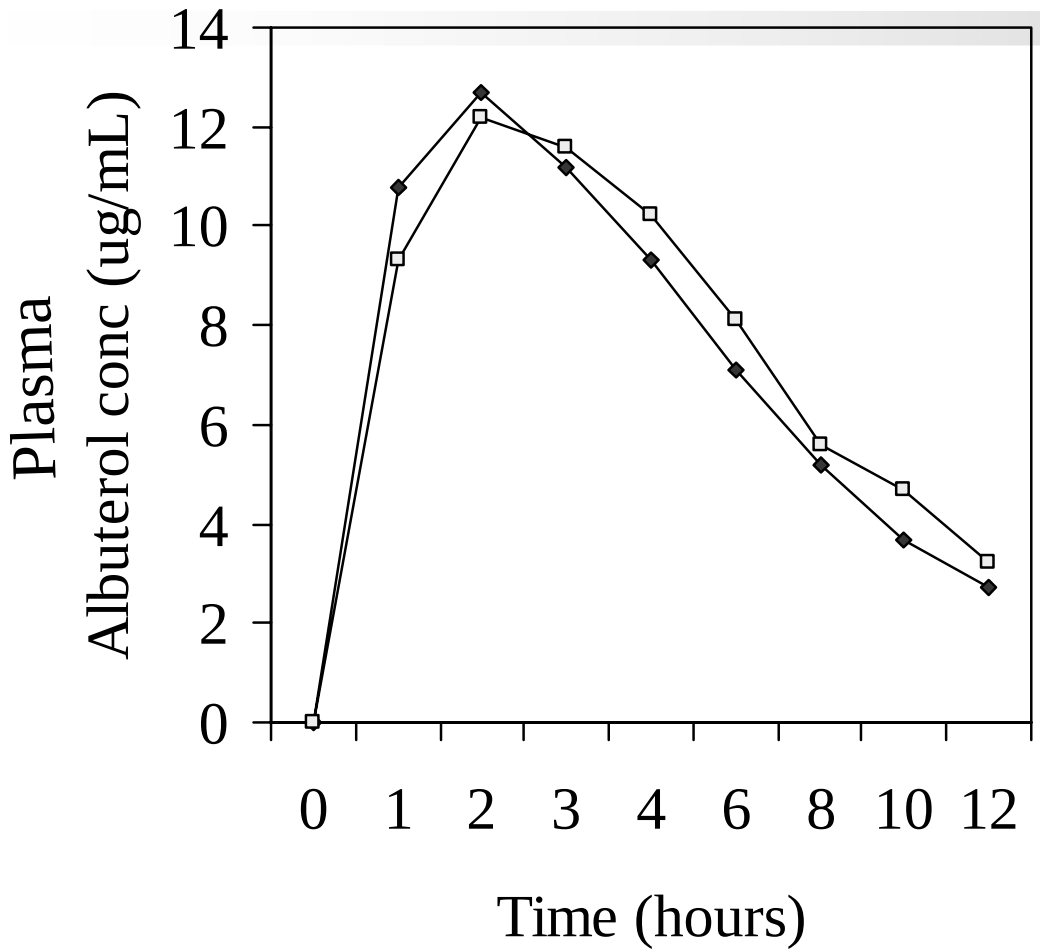
Improving risk and benefit through pharmacogenetics

Pharmacokinetic variability
Managed by dose adjustment

Pharmacodynamic variability
Manageable generally only by modulating a different pharmacological target

β2-adrenoreceptor polymorphisms

Lima JJ et al, Clin Pharmacol Ther, 1999; 65: 519-525



Pharmacokinetics

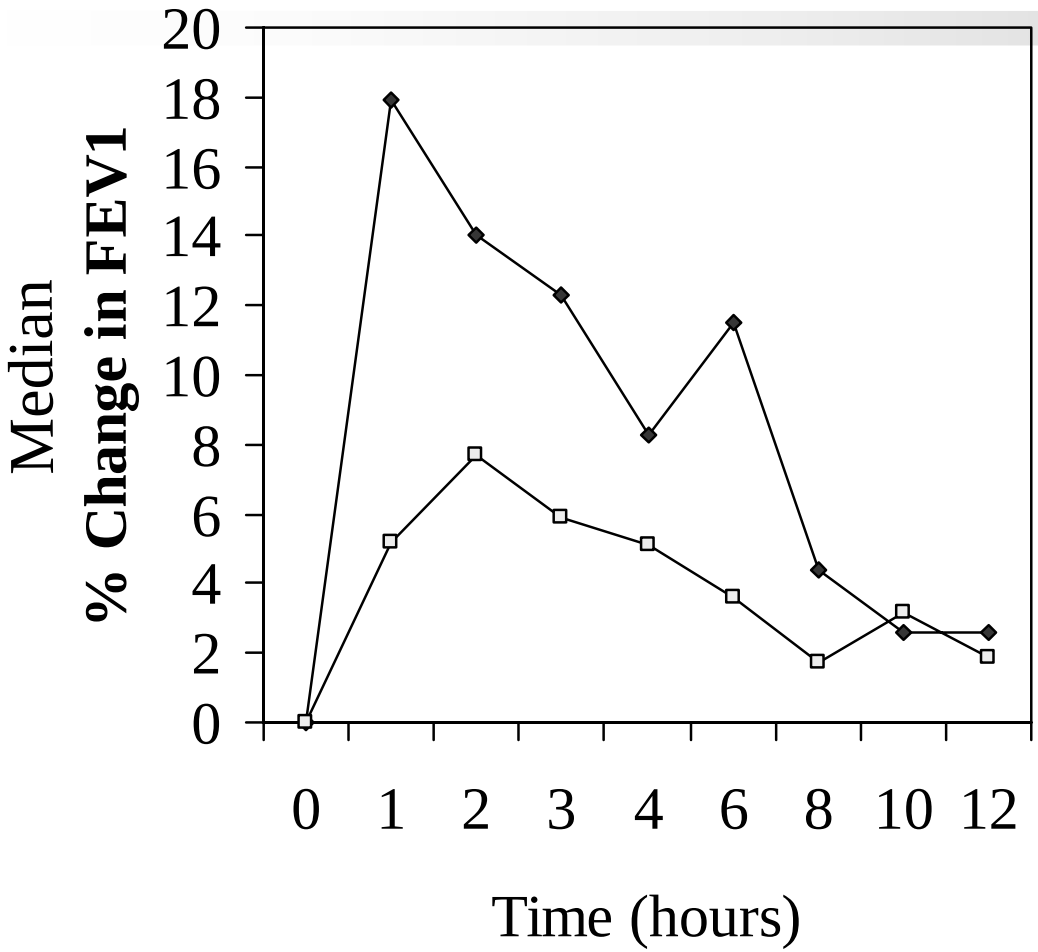
Arg16/Arg16

Arg16/Gly16 and Gly16/Gly16

Mean of 16 patients with moderate asthma following a single oral dose of 8mg

β2-adrenoreceptor polymorphisms

Lima JJ et al, Clin Pharmacol Ther, 1999; 65: 519-525



Pharmacodynamics

- Arg16/Arg16
- Arg16/Gly16 and Gly16/Gly16

Mean of 16 patients with moderate asthma following a single oral dose of 8mg

β2-adrenoreceptor polymorphisms

Some β1-adrenoceptor or β2-adrenoceptors polymorphisms have been related to survival in patients with cardiac failure

β2-adrenoceptor polymorphism also influences therapeutic response to carvedilol. Patients who are homozygous for Gln27 display a significantly lower proportion of good responders than patients who are homozygous or heterozygous for the Glu27 polymorphism (26% versus 63%)

Depression is a heterogeneous disease

Genetic variation of serotonin transporter is involved in clinical remission of major depressive episodes after twelve weeks of **citalopram** treatment (Arias et al, 2003)

The **short allele** of the 5HTTLPR may identify patients at risk for developing **insomnia or agitation** with **fluoxetine** treatment
(Perlis et al, 2003)

Subjects homozygous for the **long allele** of 5HTTLPR showed a significantly **faster response** to **sertraline** or **paroxetine**
(Durham et al, 2004; Pollock et al, 2000)

Lack of LL genotype = Lack of response (in 83.3%)
(Kim et al, 2000)

Improving risk and benefit through pharmacogenetics

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Pharmacokinetic versus Pharmacodynamic Polymorphisms

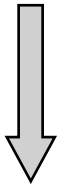
Pharmacokinetic polymorphisms appear more important	Pharmacodynamic polymorphisms appear more important
	HMG-CoA reductase inhibitors
‘Setrons’	‘Setrons’
	SSRI antidepressants
	Other antidepressants
Carvedilol	Carvedilol, metoprolol
	Salbutamol (β2-agonists)
	Warfarin
Neuroleptics	Neuroleptics

Potential case for a genetic substrate in drug-induced TdP

Drug	Without risk factor
Cisapride	**38/341 (11 %)** (Wysowski D et al, 2001)
Terodiline	**12/69 (18 %)** (Shah RR, 2002)
Prenylamine	**30/158 (19 %)** (Shah RR, 2002)
Miscellaneous	**10-15 %** (Yang P et al, 2002)

Potential case for a genetic substrate in drug-induced TdP

105 patients with AF treated with dofetilide



7 developed torsade de pointes

- **2/7 (28.5%) with TdP had R1047L hERG channel**
- **5/98 (5.1%) without TdP had R1047L hERG channel**

Sun Z et al, 2004

Potential undesirable consequence of Pharmacogenetics in therapeutics

Trying to avoid:

EM
PM: Overdosing to prevent ADRs

Potential undesirable consequence of Pharmacogenetics in therapeutics

Do not end with:

EM: Under-dosed with loss of efficacy
PM: Overdosing to prevent ADRs

Data on irinotecan not robust enough to make dosing recommendations on the basis of UGT1A1 genotype

Improving risk and benefit through pharmacogenetics

Threats to benefits from pharmacogenetics

Ethnic differences in allele frequencies
Promotion of high doses
Drug interactions
Disregard of prescribing information
Gene-gene interactions
Lack of or poor genotype-phenotype correlation
Clinical motivation and practicalities

Pharmacogenetics versus drug interactions

A 74-year-old woman with high cholesterol.
Cerivastatin (0.15 mg/day) for 22 days

Rhabdomyolysis (Serum CPK 19,190 IU/L and myoglobin > 3000 ng/mL)

Serum concentration of cerivastatin at 6 h after taking the last dose (0.15 mg) was 8062.5 ng/L (5.7-fold higher than normal)
Half-life of cerivastatin in this patient was 22.4 h (normal 2.4 h)
Three nucleotide variants, 475delA, G874C, and T1551C, were found in the exons of CYP2C8. The patient's children were both heterozygous for the mutation.
Previously taken simvastatin without any problems.

These results suggest that the slowed clearance of cerivastatin in this patient might have been compounded by CYP2C8 dysfunction.

Ishikawa C et al, J Hum Genet. 2004;49(10):582-5.
Ozaki H et al, J Clin Pharm Ther. 2005 Apr;30(2):189-92.

Pharmacokinetics and safety

No evidence from prospective controlled studies to suggest that routine genotyping for drug metabolising enzymes prior to commencing therapy is helpful or cost-effective

Benefits in clinical practice

Adherence to prescribing information

- Poor track record

Contraindications:

- Terfenadine
- Cisapride
- Cerivastatin
- Bromfenac

Monitoring requirements

- Troglitazone
- Antipsychotics

The CIOMS Report

Towards improving treatment with medicines

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The extent to which this promise of pharmacogenetics is fulfille remains to be seen. The experience to date is mixed with a few successes but many frustrations. Discovering highly predictive genotype-phenotype associations during drug development an demonstrating their clinical validity and utility in well-designed prospective clinical trials will no doubt better define the role of pharmacogenetics in future clinical practice. In the meantime, pharmacogenetic research deserves support from all concerne but without unrealistic expectations.

The Royal Society Report

Personalised medicines: hopes and realities

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Pharmacogenetics is unlikely to revolutionise or personalise medical practice in the immediate future.

Rather, as related research identifies sub-groups of common diseases based on different genetic or environmental causes, and knowledge of pharmacogenetics advances, it should become possible to introduce genetic testing to predict people's response to at least some drugs. Appropriate trials and cost analyses will first have to be performed on a case-by-case basis.

Ladies and Gentlemen…

Many thanks for your kind attention