Personalized medicines: Lessons from neuropsychiatric pharmacogenetics

David Goldstein

Center for Population Genomics and Pharmacogenetics

Institute for Genome Sciences & Policy

Duke University Medical Center

Antipsychotic "effectiveness"

CLINICAL ANTIPSYCHOTIC TRIALS OF INTERVENTION EFFECTIVENESS

- **The CATIE trial compared the effectiveness of atypical antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone) with perphenazine in 1493 patients from 57 US clinical sites**

Discontinuation

- Olanzapine   64
- Quetiapine   82
- Risperidone   74
- Ziprasidone   79

- Perphenazine   75

And end to the blockbuster era?

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  - 30 % of patients on olanzapine increase body wt > 7%
  - Similar proportion on many of the typical antipsychotics develop TD

Can pharmacogenetics help?

- Genetic differences may predict efficacy and sensitivity to adverse reactions and efficacy

- Genetic differences may predict appropriate doses for individual patients

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- *There have been no serious efforts to find such variants for the vast majority of marketed medicines*

Lessons from Anti Epileptic Drugs

Carbamazepine and Phenytoin

- Widely used (especially Carbamazepine)
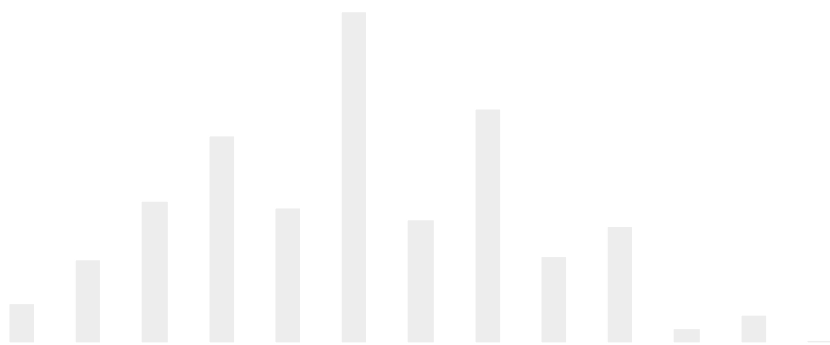
- Inexpensive

- Effective

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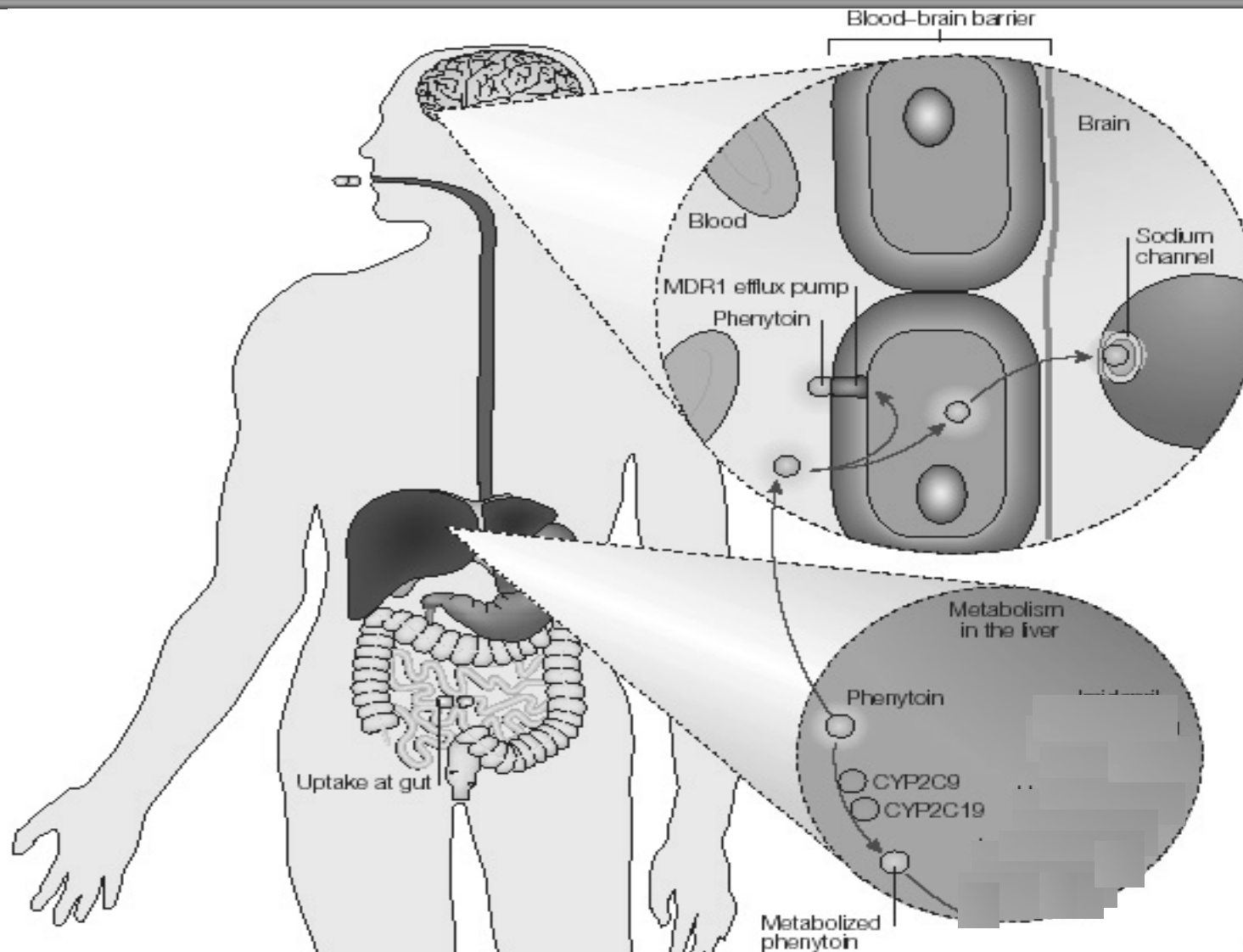- **Appropriate doses can take months to find**

Maximum doses

Phenytoin
(n=269)

Carbamazepine
(n=425)

Phenytoin Pathway

Tagging SNPs
to represent common (known & unknown) variation

Haplotype

1	C	C	T	T	T	A	C	C	C	T	T	C
2	C	C	T	T	T	A	C	C	C	T	A	A
3	C	G	T	T	A	G	C	G	C	T	T	C
4	T	C	T	T	T	A	C	C	G	T	T	C
5	T	C	A	A	A	G	G	G	A	T	C	

Haplotype

1	C	C	T	T	T
2	C	C	T	T	A
3	C	G	T	A	T
4	T	C	T	T	T
5	T	C	A	A	T

Results

CYP2C9 Allele	Freq. (%)	Average Phenytoin Dose (mg)			Sig.
		wt/wt	wt/var	var/var	
*2	11.9	357	339	317	0.38
*3	9.7	362	304	250	**0.005**

SCN1A – "tag 7"

	AA	AG	GG	Significance
Phenytoin	373	340	326	p=0.005
Carbamazepine	1312	1225	1083	p=0.001

tSNP7 may affect SCN1A splicing in humans

Adult

exon 4 | exon 5A | exon 6

exon 4 | exon 5N | exon 5A | exon 6

tSNP7 A

Neonate

exon 4 | exon 6
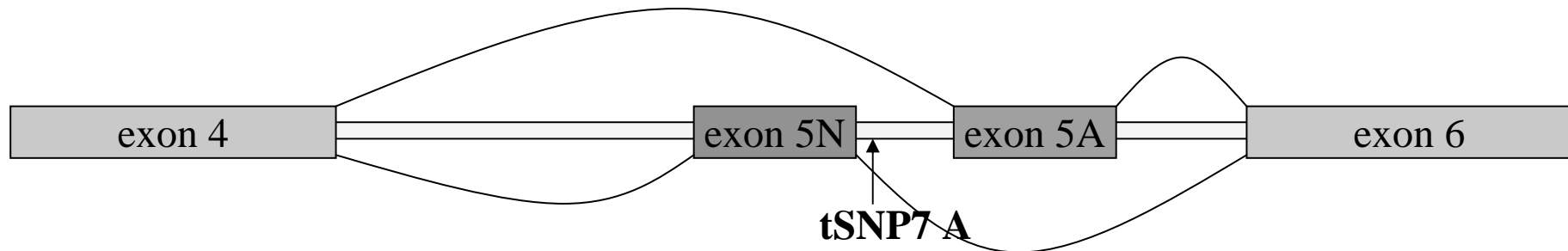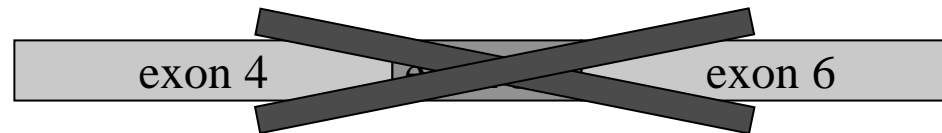
tSNP7 A = splice site disrupted, expression of exon 5N altered altered 5A/5N ratio?

Exon 5N is up-regulated in SCN genes in human epileptic tissues
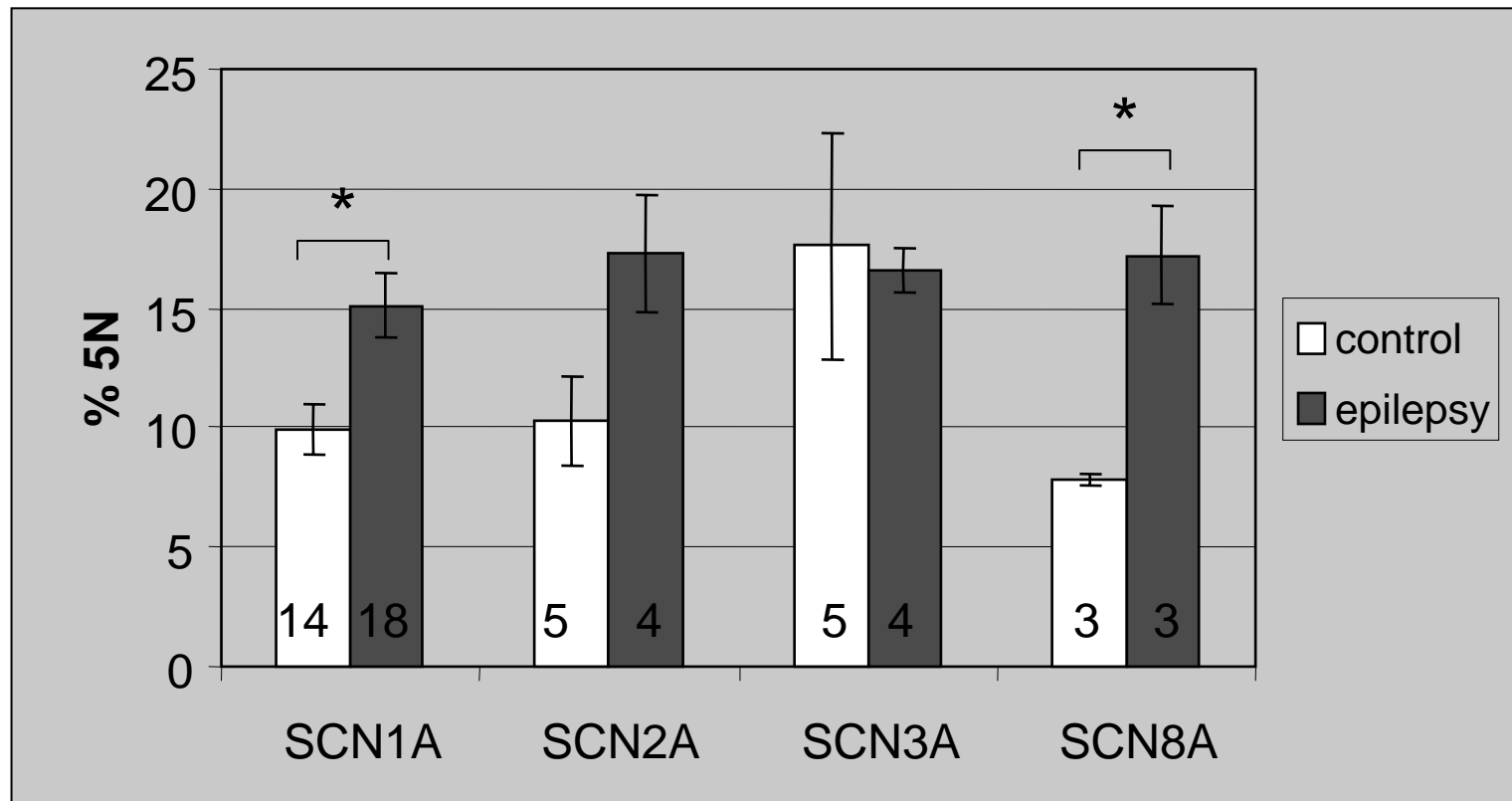
- Control RNA was purified from tissues in the Parkinson's Brain Bank
- For all but SCN1A, sample sizes are small
- SCN5A and SCN9A were not reliably detected in these tissues

Pharmacogenetics
What is needed?

Patients Cohorts

- Standard measures of clinical responses (all aspects)
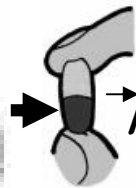- Sufficient numbers to accommodate clinical complexity and identify variants of modest effect

- Whenever large cohorts have been assembled, with carefully assessed drug responses measures, gene variants are identified that influence response
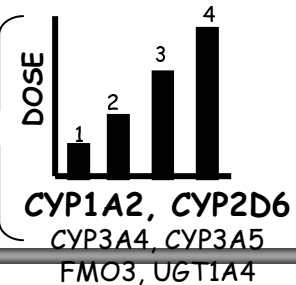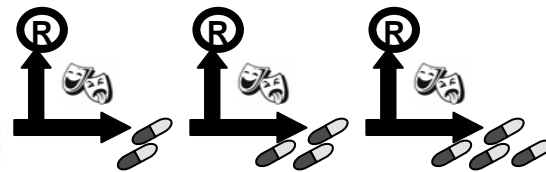
Pharmacogenetics of dosing

CATIE
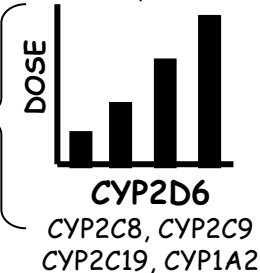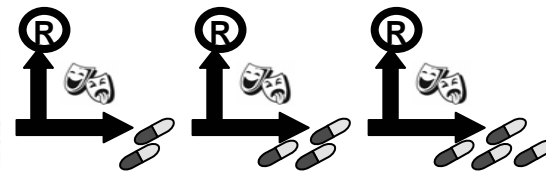Clinical Antipsychotic Trials of Intervention Effectiveness
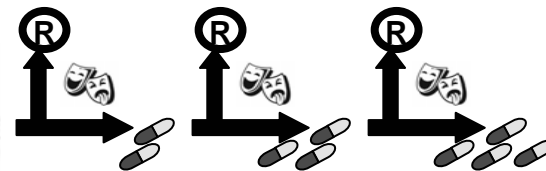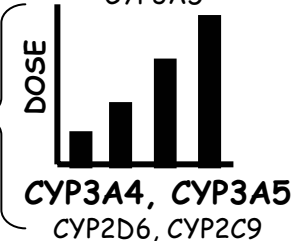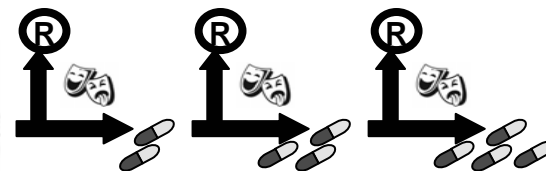
1600 patients with Schizophrenia

Olanzapine
5mg/day

DOSE
1 2 3 4

CYP1A2, CYP2D6
CYP3A4, CYP3A5
FMO3, UGT1A4

Perphenazine
8mg/day

DOSE

CYP2D6
CYP2C8, CYP2C9
CYP2C19, CYP1A2

Risperidone
1.5mg/day

DOSE

CYP2D6
CYP2C9, CYP3A4
CYP3A5

Quetiapine
200mg/day

DOSE

CYP3A4, CYP3A5
CYP2D6, CYP2C9

Ziprasidone
40mg/day

DOSE

CYP3A4, CYP3A5
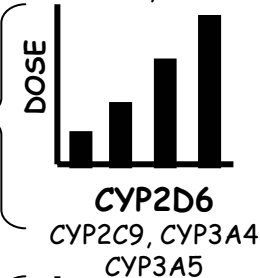
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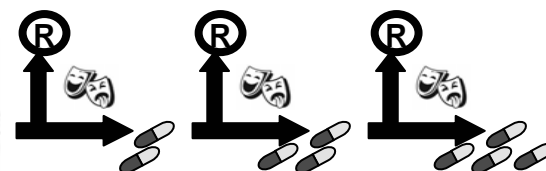
- It is reasonable to conclude that a careful pharmacogenetic study would lead to improvements in the clinical use of most medicines

Pharmacogenetics
What is needed?

Well defined pathways providing compelling candidate genes

- *Pharmacodynamics:*
- *Pharmacokinetics*: drug metabolizing enzymes, transporters
- Genes known to affect pathways relevant to *ADRs*, e.g. weight gain, long QT syndrome

Pharmacogenetics
What is needed?

Systematic characterisation of candidate genes

- Analyse all relevant genes in pathway, not just famous ones
- Analyse all variants in the genes, (including variation from multiple populations if sample is mixed) until knowledge permits study of only functionals
  - tagging
- Gene-gene interactions
- Gene-environment interactions

Pharmacogenetics
What is needed?

Best practise

– Stratification checks

  • Genomic control

  • Ancestry informative markers

– Replication, replication, replication

– Functional follow-up of implicated variants

  • Alternative splicing, expression, activity, abundance/ distribution of protein

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