CYTOCHROMES SIMPLIFIED: AN INTRODUCTION TO GENETIC INFLUENCES ON DRUG METABOLISM

Timothy Dellenbaugh, M.D.
Residency Director
Associate Professor of Psychiatry
University of Missouri-Kansas City
Assistant Medical Director
Center for Behavioral Medicine

At the conclusion of the activity, the participant will be able to:

1. discuss genetic influences on psychiatric drug metabolism through Cytochrome P450 2D6
2. summarize genetic causes and clinical implications of 2D6 phenotypes: ultra-rapid, extensive, intermediate, and poor
3. develop strategies for learning cytochrome-based drug interactions

Important but not covered

- Receptor variations (Pharmacodynamics)
  - D2, D4, 5HT2a, etc
- Reuptake pumps
  - DA, 5HT
- ABC transporters

Definitions

- Substrate
- Inhibitor
- Inducer

Smokers need higher than typical doses of most antipsychotics

- T/F

How quickly does starting an Inhibitor cause change in metabolism?

A. Depends on ½ life of substrate

B. Depends on ½ life of inhibitor

C. Depends on ½ life of cytochrome

D. Depends on rate of cytochrome production

How quickly does stopping an Inhibitor cause change in metabolism?

A. Depends on ½ life of substrate

B. Depends on ½ life of inhibitor

C. Depends on ½ life of cytochrome

D. Depends on rate of cytochrome production

A potent inhibitor decreases cyp 2D6 activity for which groups?

A. ultra-rapid

B. extensive

C. intermediate

D. poor

E. all groups would decrease

How quickly does stopping an inducer cause change in metabolism?

A. Depends on ½ life of substrate

B. Depends on ½ life of inhibitor

C. Depends on ½ life of cytochrome

D. Depends on rate of cytochrome production

How many genetic variants of 2D6 have been identified?

A. 5-10

B. 10-25

C. 25-50

D. 50-100

E. >100

What is Cytochrome P450 2D6 *1

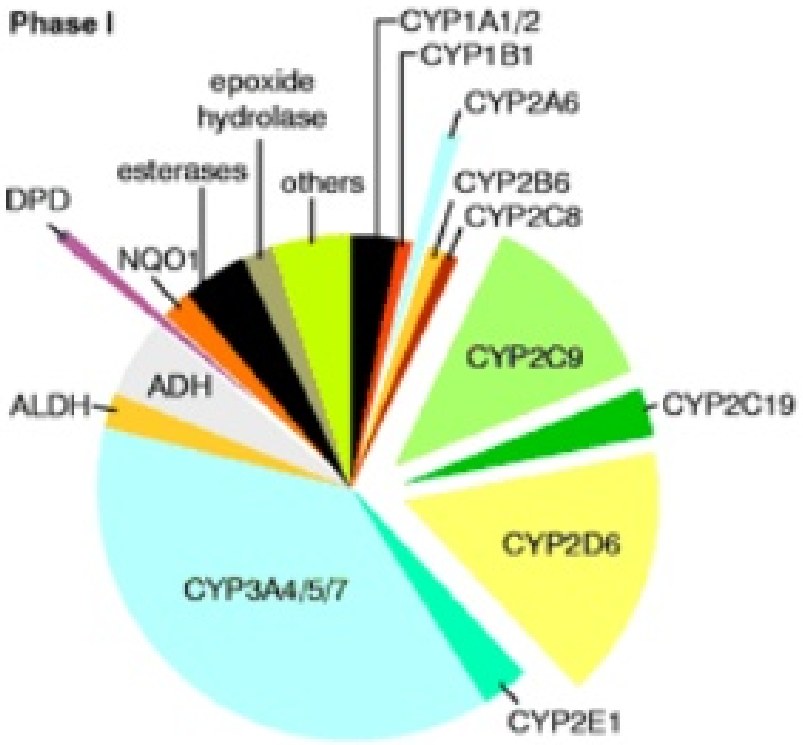
- Cytochrome
  - What does it do?
  - Why named P450?
    - Superfamily
- Family- >40% AA identity
  - CYP1, CYP2
- Subfamily- >55% A,B,C,D
- Individual Loci- 1,2,3
- Alleles- >97%- *1, *2, *41

Total cyp 2D6 activity depends on which of the following?

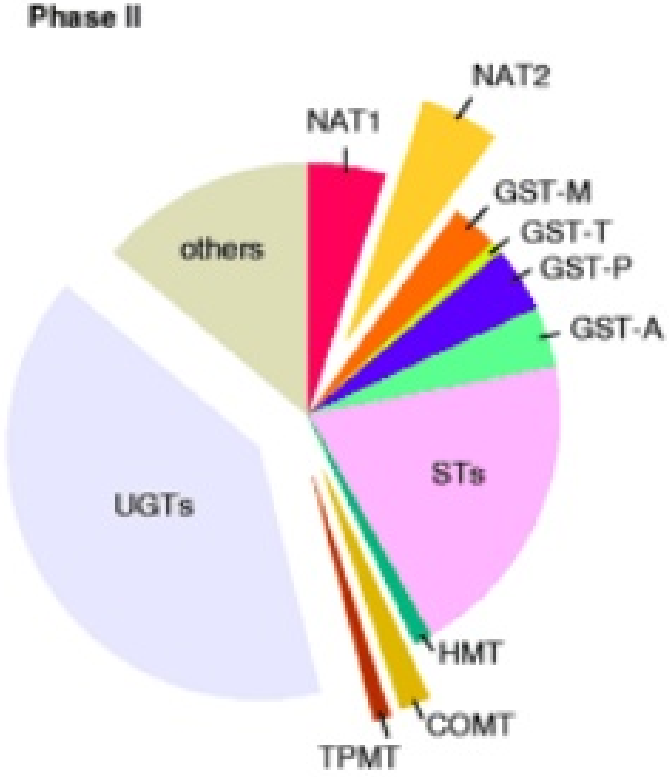
- Which dominant allele is inherited
- Which pair of alleles are inherited

- How much 2D6 is produced
- Which variations of 2D6 are produced

Drug-Metabolizing Enzymes



Phase I: modification of functional groups

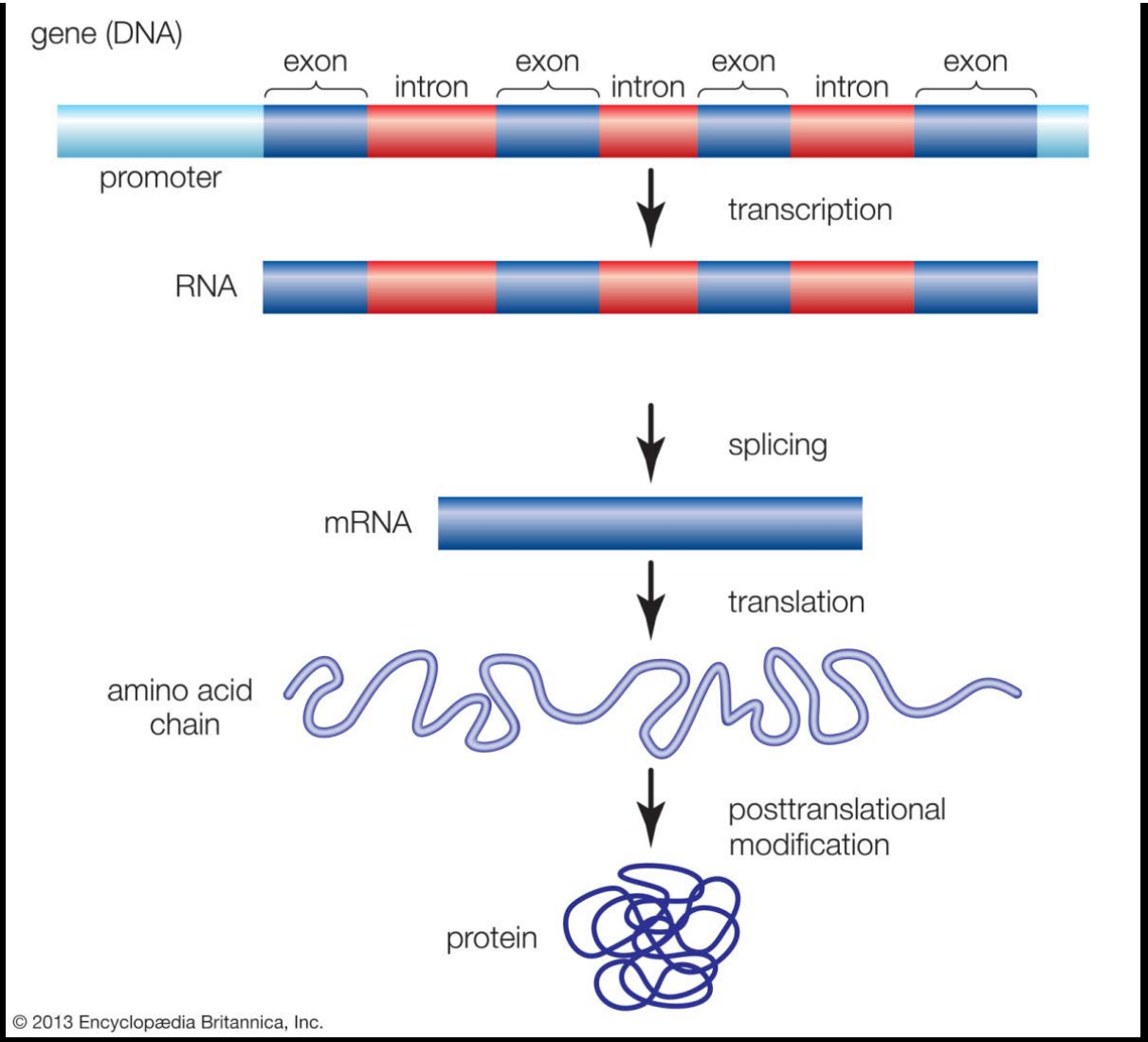


Phase II: conjugation with endogenous substitutents

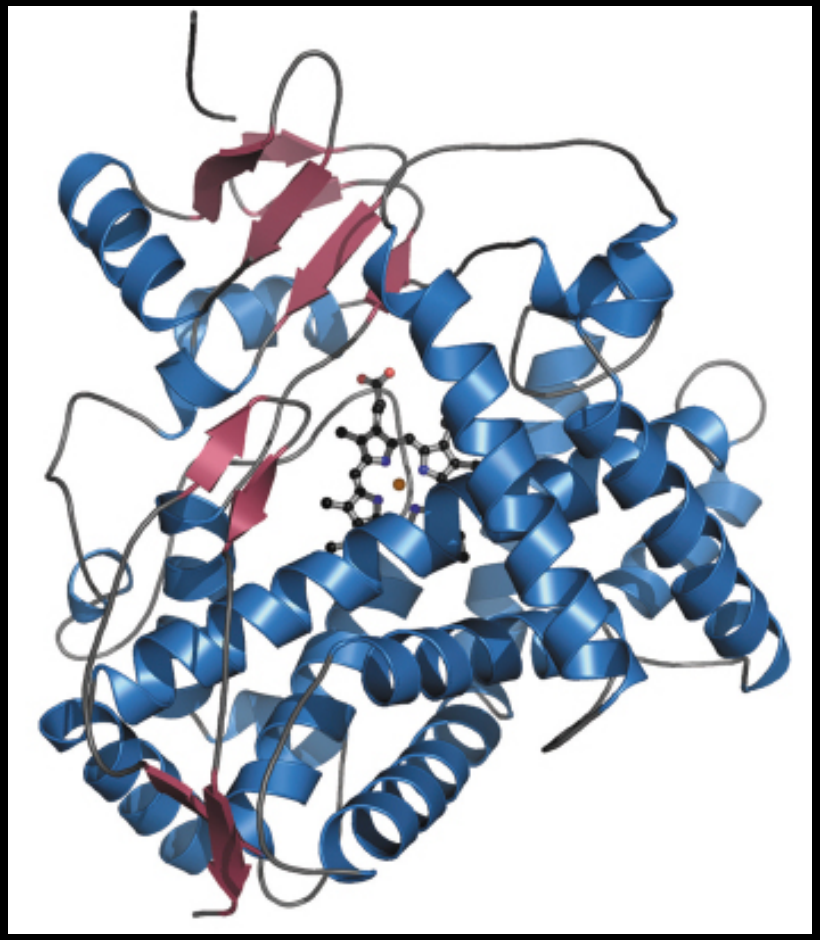
Most DME have clinically relevant polymorphisms
Those with changes in drug effects are separated from pie.

Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics. Evans and Relling Science 1999

Enzyme synthesis



2D6



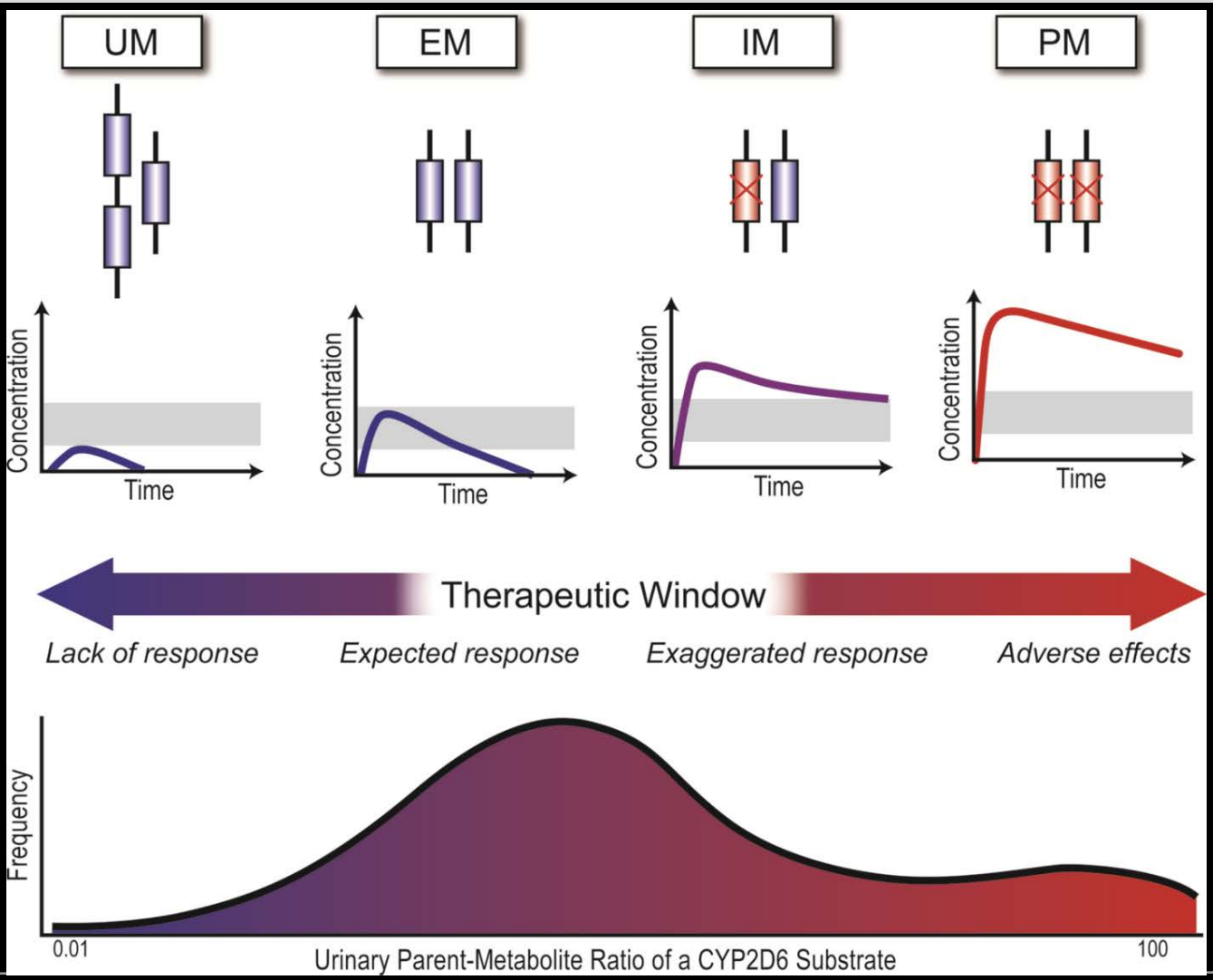
CYP2D6

- highly polymorphic gene
- >130 genetic variations described
- Duplication
- Deletion
- Splice defect
- SNP

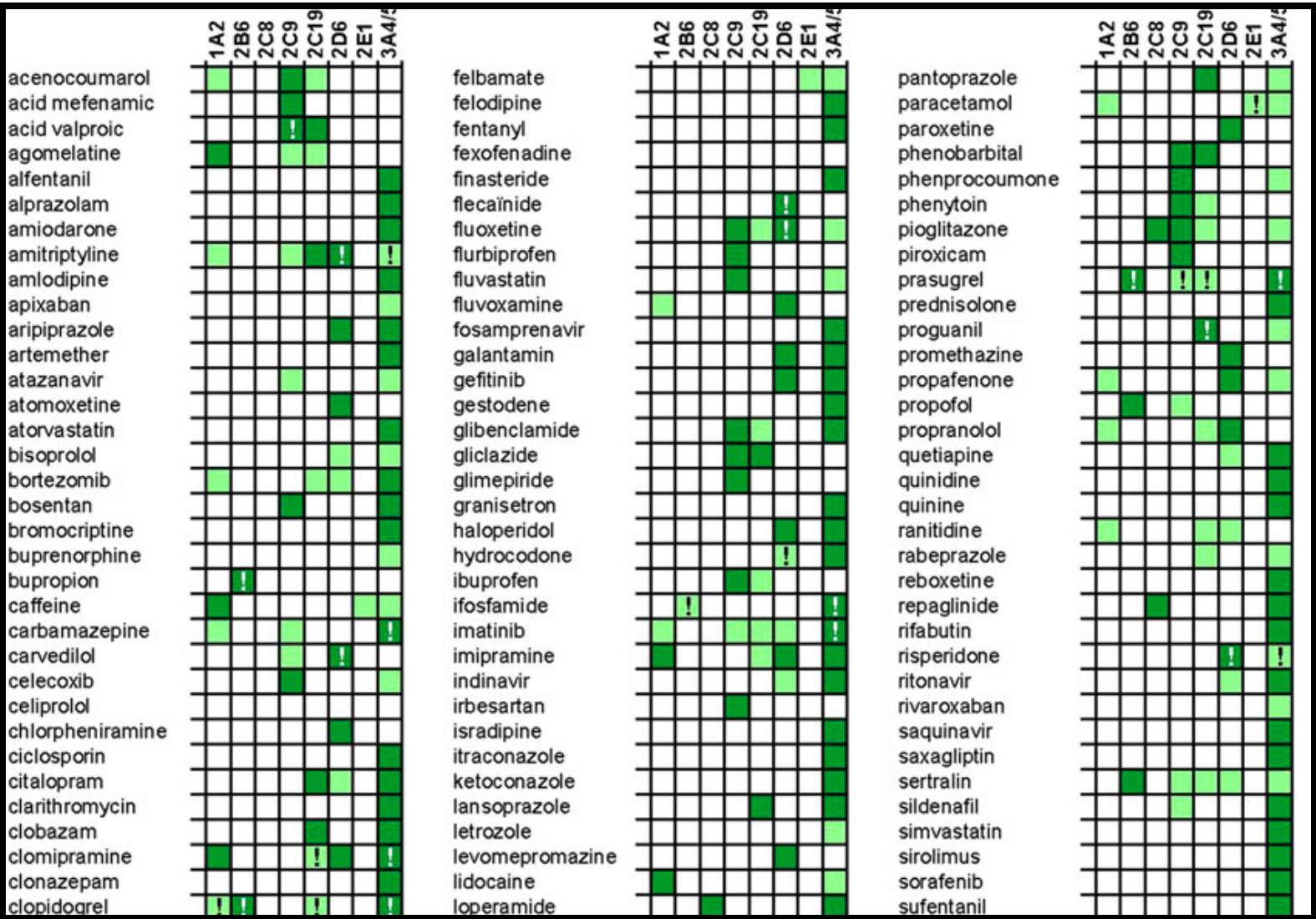
ANESTHESIOLOGY
The Journal of the American Society of Anesthesiologists, Inc.

From: Genetic Variation, β-blockers, and Perioperative Myocardial Infarction

Anesthesiology. 2011;115(6):1316-1327. doi:10.1097/ALN.0b013e3182315eb2



Substrates


1A2 2B6 2C8 2C9 2C19 2D6 2E1 3A4/5
acenocoumarol
acid mefenamic
acid valproic
agomelatine
alfentanil
alprazolam
amiodarone
amitriptyline
amlodipine
apixaban
aripiprazole
artemether
atazanavir
atomoxetine
atorvastatin
bisoprolol
bortezomib
bosentan
bromocriptine
buprenorphine
bupropion
caffeine
carbamazepine
carvedilol
celecoxib
celiprolol
chlorpheniramine
ciclosporin
citalopram
clarithromycin
clobazam
clomipramine
clonazepam
clopidogrel
felbamate
felodipine
fentanyl
fexofenadine
finasteride
flecaïnide
fluoxetine
flurbiprofen
fluvastatin
fluvoxamine
fosamprenavir
galantamin
gefitinib
gestodene
glibenclamide
gliclazide
glimepiride
granisetron
haloperidol
hydrocodone
ibuprofen
ifosfamide
imatinib
imipramine
indinavir
irbesartan
isradipine
itraconazole
ketoconazole
lansoprazole
letrozole
levomepromazine
lidocaine
loperamide
pantoprazole
paracetamol
paroxetine
phenobarbital
phenprocoumone
phenytoin
pioglitazone
piroxicam
prasugrel
prednisolone
proguanil
promethazine
propafenone
propofol
propranolol
quetiapine
quinidine
quinine
ranitidine
rabeprazole
reboxetine
repaglinide
rifabutin
risperidone
ritonavir
rivaroxaban
saquinavir
saxagliptin
sertralin
sildenafil
simvastatin
sirolimus
sorafenib
sufentanil

Inhibitors

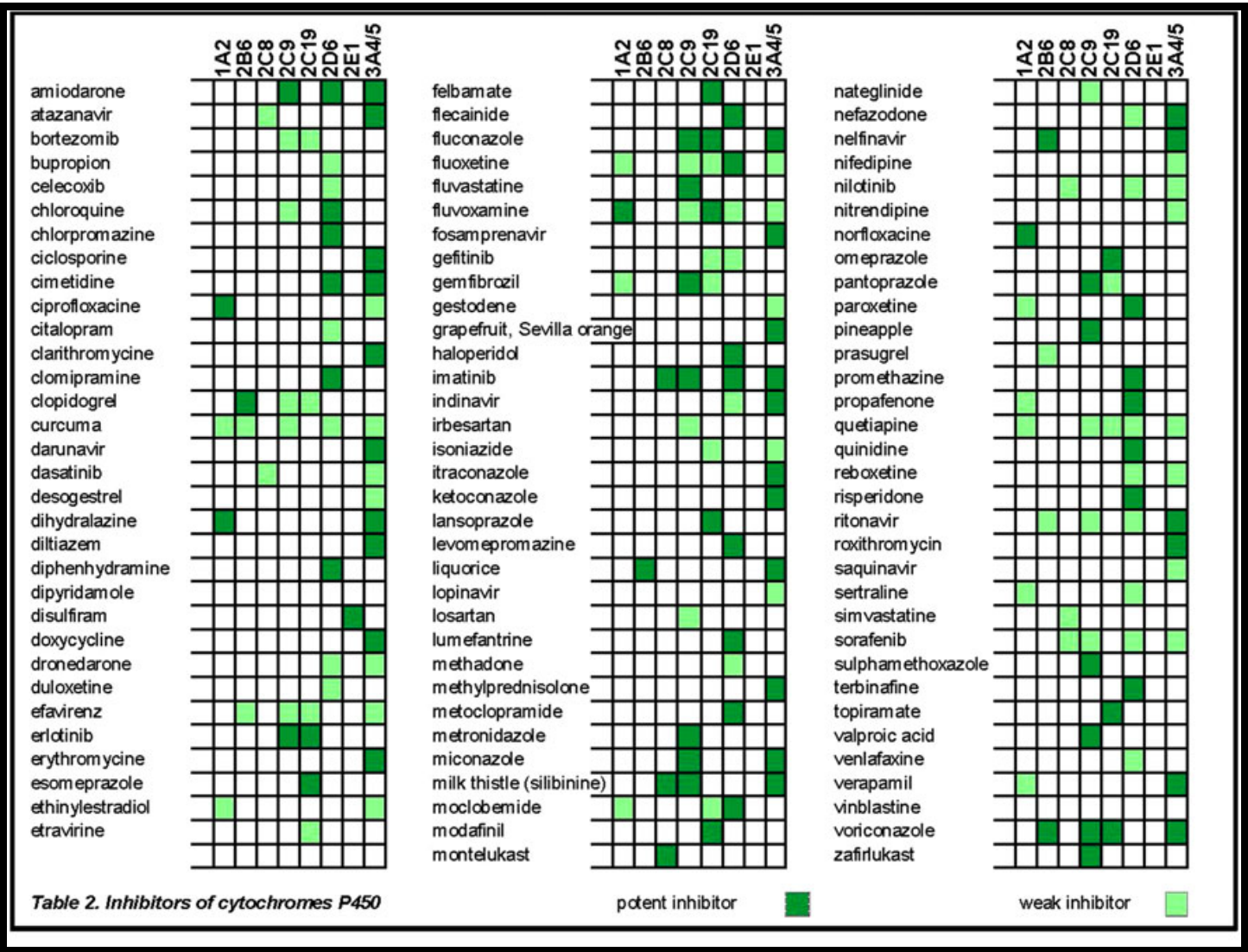


Table 2. Inhibitors of cytochromes P450

Inducers

Promote

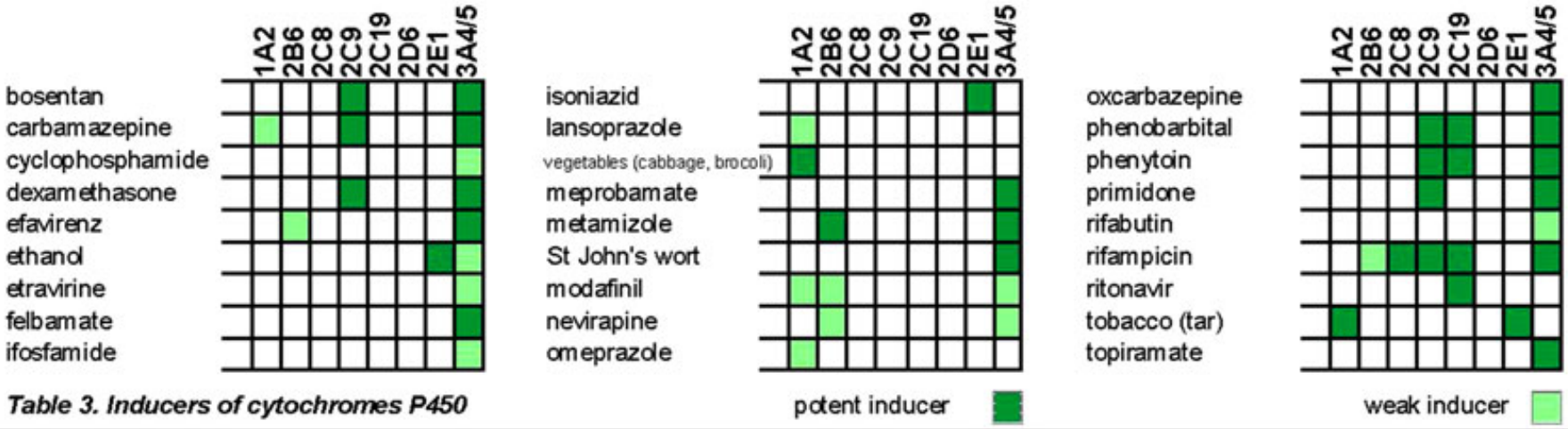


Table 3. Inducers of cytochromes P450

Inhibition

The impact depends on: **a)** relative importance of the inhibited elimination pathway, relative to the total clearance; **b)** whether active metabolites are present or not, and **c)** concentration of the inhibitor. Upon cessation of the inhibitor treatment CYP returns to its normal activity after elimination of the inhibitor (4 half-lives). *Examples* : CYP2C9 's activity is strongly inhibited by **amiodarone**. In association with **acenocoumarol**, a CYP2C9 substrate, amiodarone will slow the latter's elimination, potentially causing haemorrages, which justify adapting the posology and closely monitoring the INR. **Fluoxetine** inhibits strongly the activity of CYP2D6. In association with **codeine**, it can abolish any efficacy of the latter.

Induction

The impact depends upon: **a)** relative importance of the induced elimination pathway relative to the total clearance, **b)** whether active metabolites are present or not, and **c)** concentration of the inducer. Upon cessation of the inducer treatment CYP progressively returns to its normal activity (> 2 weeks after elimination of the inhibitor from blood).
Example: St John's Wort progressively and potently induces CPY3A4 activity. St John's Wort strongly accelerates the elimination of ethinylestradiol, a major CYP3A4 substrate, which means that contraception will not be ensured and other contraceptive means will be needed.

How to learn

- Daily use vs. episodic use
- Focus on clinical relevance
- Ignore small effects
- Organize data for visual recall
- Selective sources

Metabolic Pathways	1A2	3A4	2D6
Psychiatric Substrates			
Other Important Substrates			
Inhibitors			
Inducers			
Genetics			

Where can you find reliable and useful drug interaction data?

- http://medicine.iupui.edu/clinpharm/ddis/main-table/
- http://www.fda.gov/
- https://www.pharmgkb.org/index.jsp

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D. Depends on rate of cytochrome production

A potent inhibitor decreases cyp 2D6 activity for which groups?

A. ultra-rapid-yes

B. extensive-yes

C. intermediate-yes

D. poor-no,
it's already broken

How quickly does stopping an inducer cause change in metabolism?

A. Depends on ½ life of substrate

B. Depends on ½ life of inhibitor

C. **Depends on ½ life of cytochrome**

D. **Depends on rate of cytochrome production**

How many genetic variants of 2D6 have been identified?

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E. **>100**

References

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