Drug Interactions with Smoke and Smoking Cessation Medications

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Disclosures

- Advisory Boards
  - Amgen, AstraZeneca, BMS, Janssen, Novartis, Pfizer, Sanofi
- Research Funding
  - Heart & Stroke, CIHR
- Professional Affiliations:
  - CACR, CCN, CDA

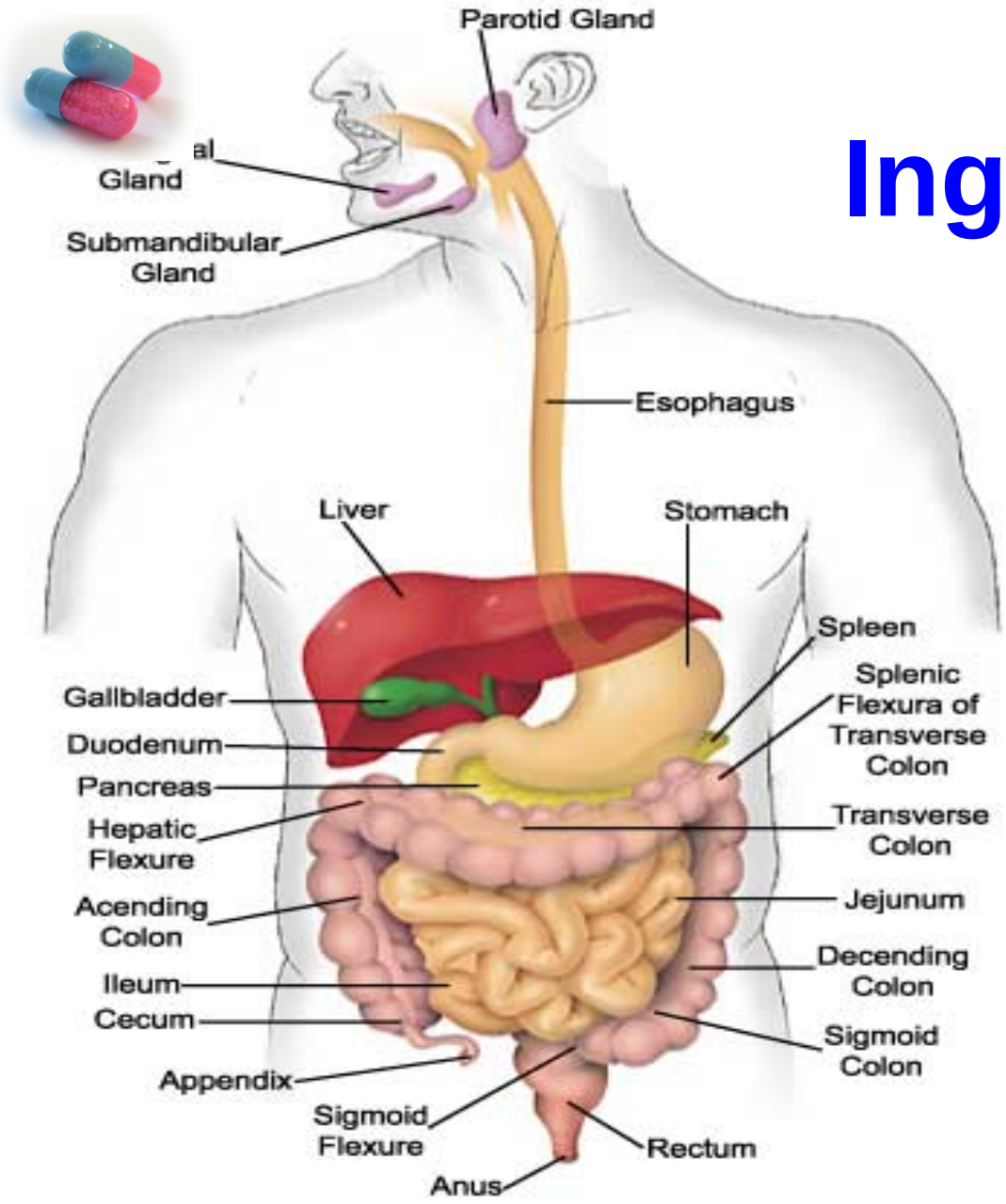
Objectives

- review pharmacokinetic principles – what is the disposition of a medication once ingested?
- highlight the role of the drug metabolism cytochrome P450 system as a particular site for many important drug interactions
- Case based discussion of common interactions – drug-drug (SCT) and drug-smoke

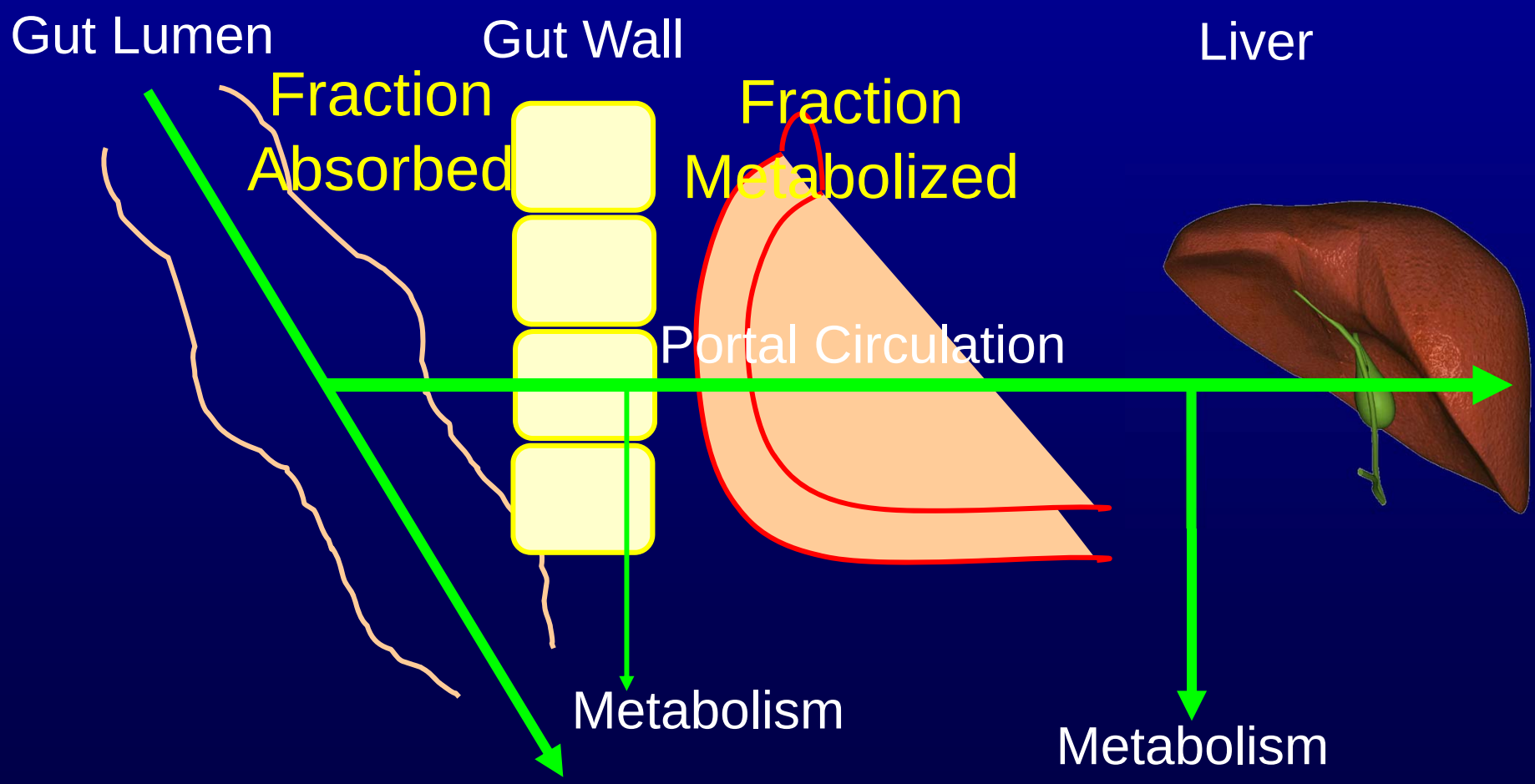
Cased Based Questions

1. What is a “CYP” and what does it do?
2. How can a sinus infection make you pass out?
3. Why is this workout so painful?
4. How do cigarettes and coffee go together?
5. Why is quitting possibly hazardous to your drug health?
6. What makes someone with heart disease and depression slow down?

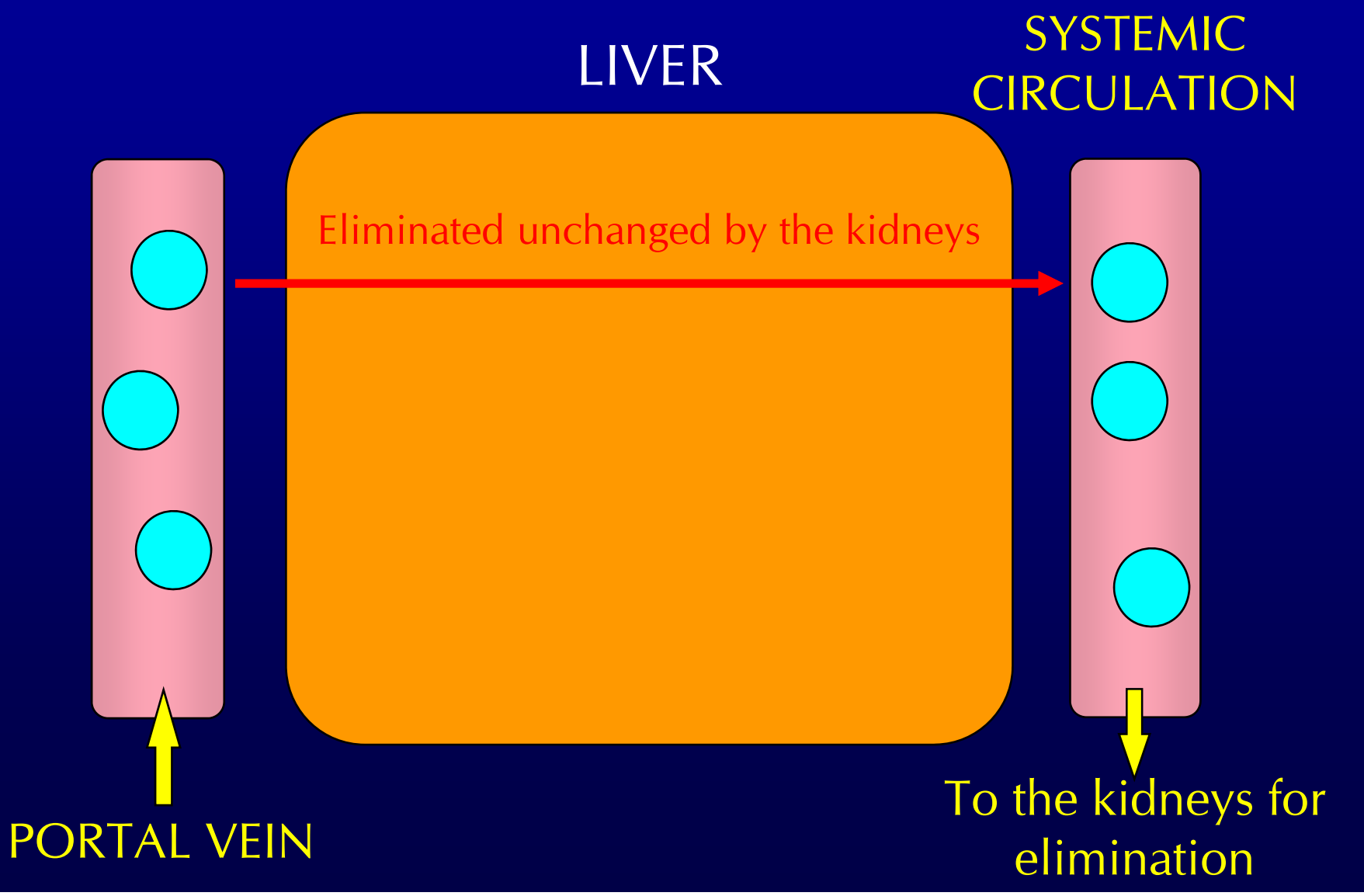
Ingestion


Parotid Gland
Gland
Submandibular Gland
Esophagus
Liver
Stomach
Spleen
Splenic Flexura of Transverse Colon
Gallbladder
Duodenum
Pancreas
Hepatic Flexure
Transverse Colon
Acending Colon
Jejunum
Decending Colon
Ileum
Cecum
Sigmoid Colon
Appendix
Sigmoid Flexure
Rectum
Anus

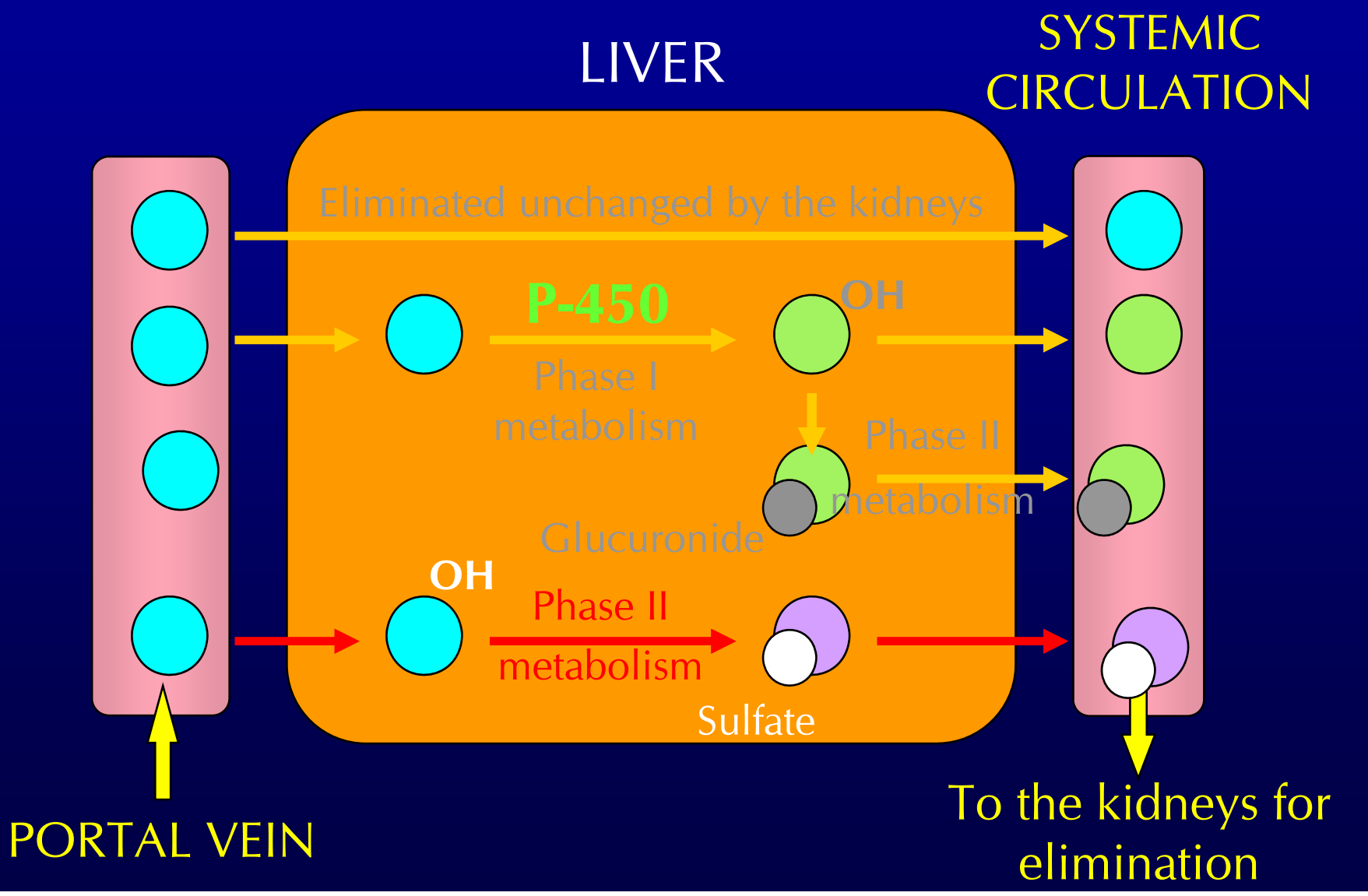
First-Pass Metabolism

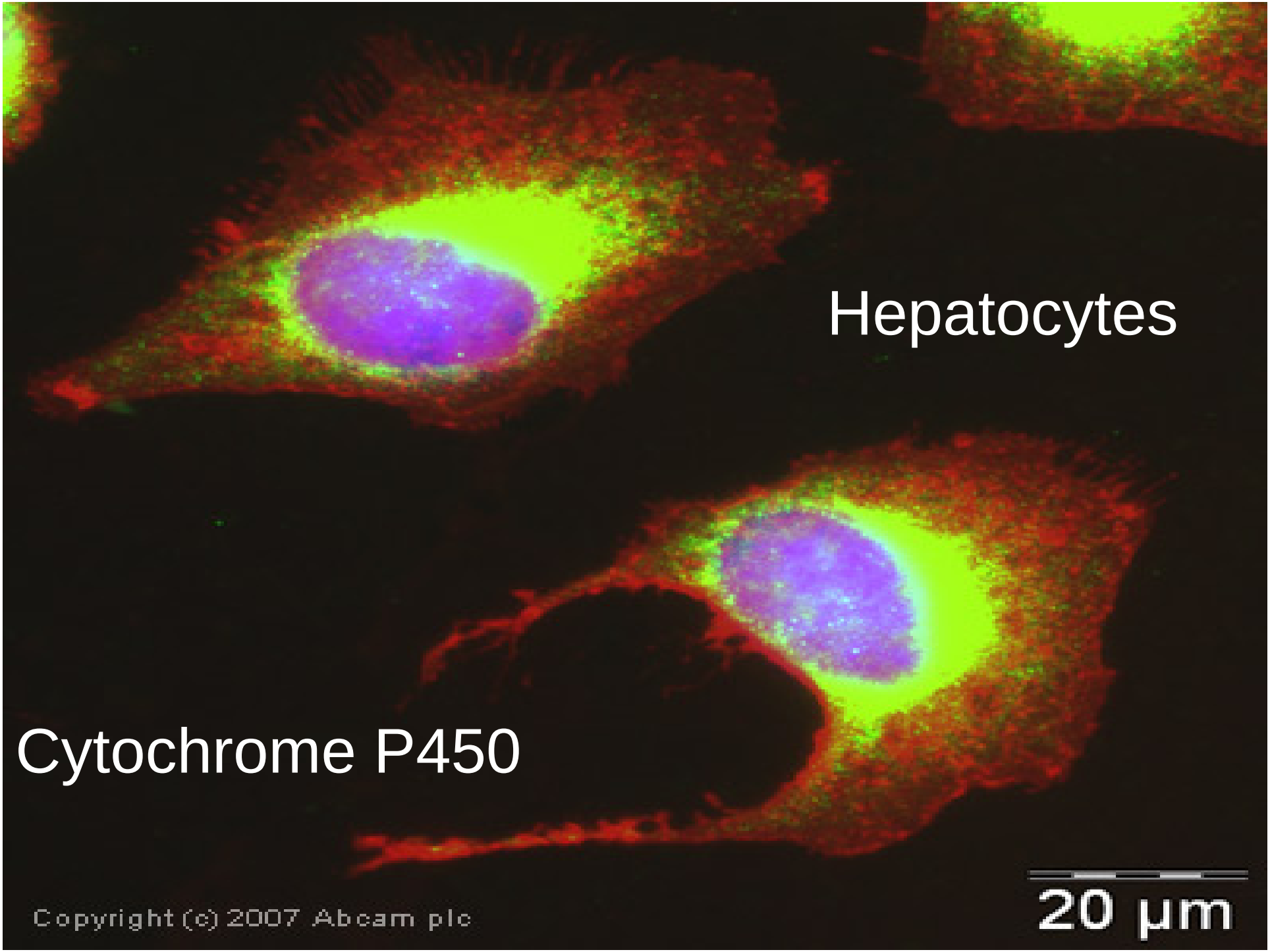


Drug Metabolism in the Liver



Drug Metabolism in the Liver




Hepatocytes
Cytochrome P450
Copyright (c) 2007 Abcam plc
20 µm

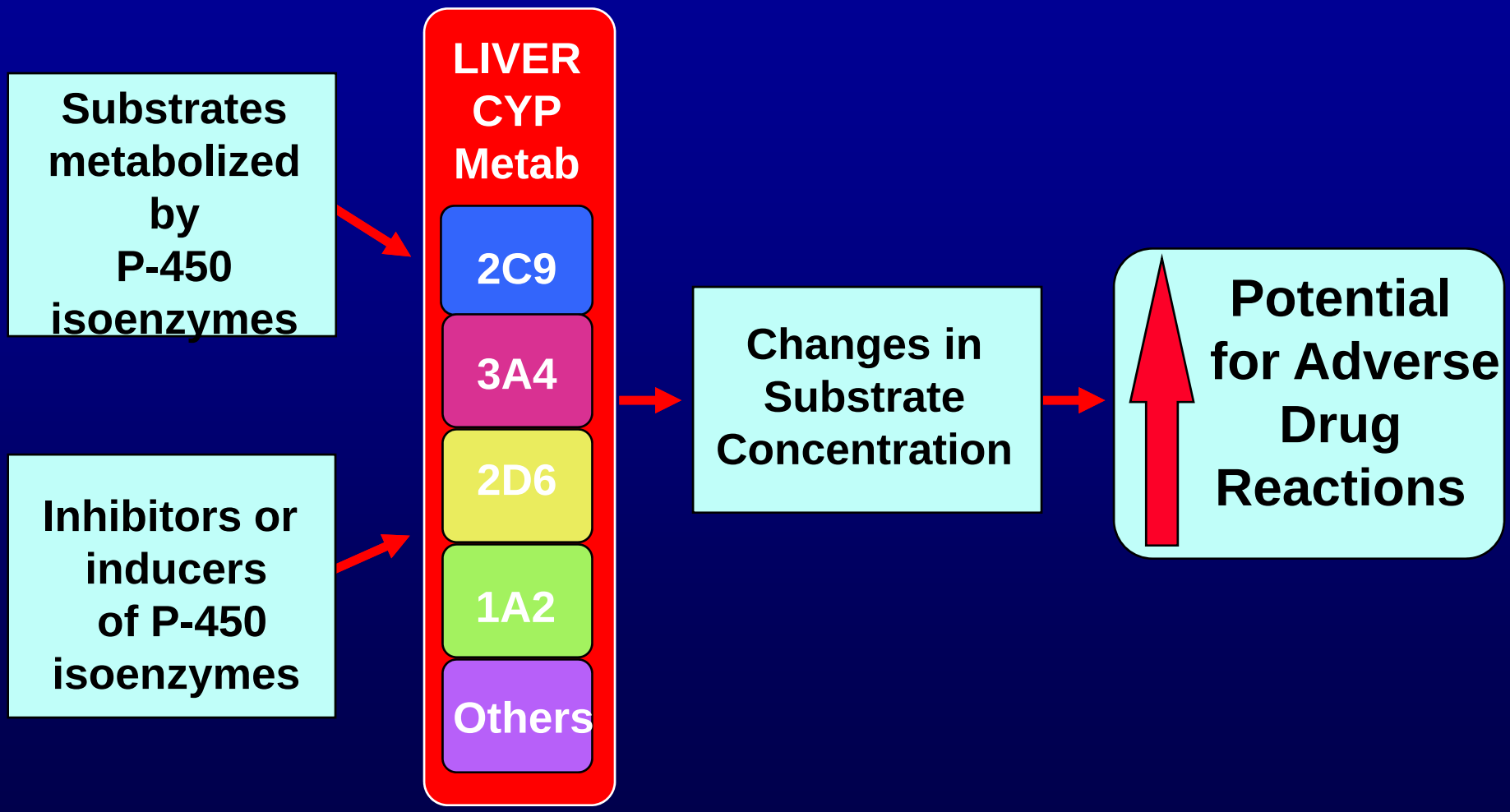
Overview of Pharmacology Concepts

Cytochrome P450 System

- Nomenclature: e.g., CYP3A4
  - "CYP" = cytochrome P450 protein abbreviation
  - family; subfamily; isoform
- The most important isoforms are **CYP3A4, CYP2D6, CYP1A2**
  - anticipate drug interactions if prescribing drugs using these enzymes.


South Africa Climate Change Response Expo

Traffic at the Cytochrome P450 Enzymes



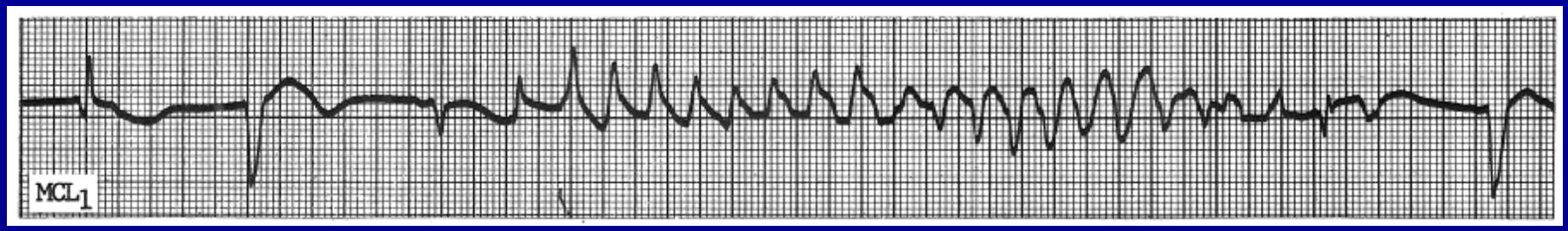
Case Study: A Lethal Sinus Infection

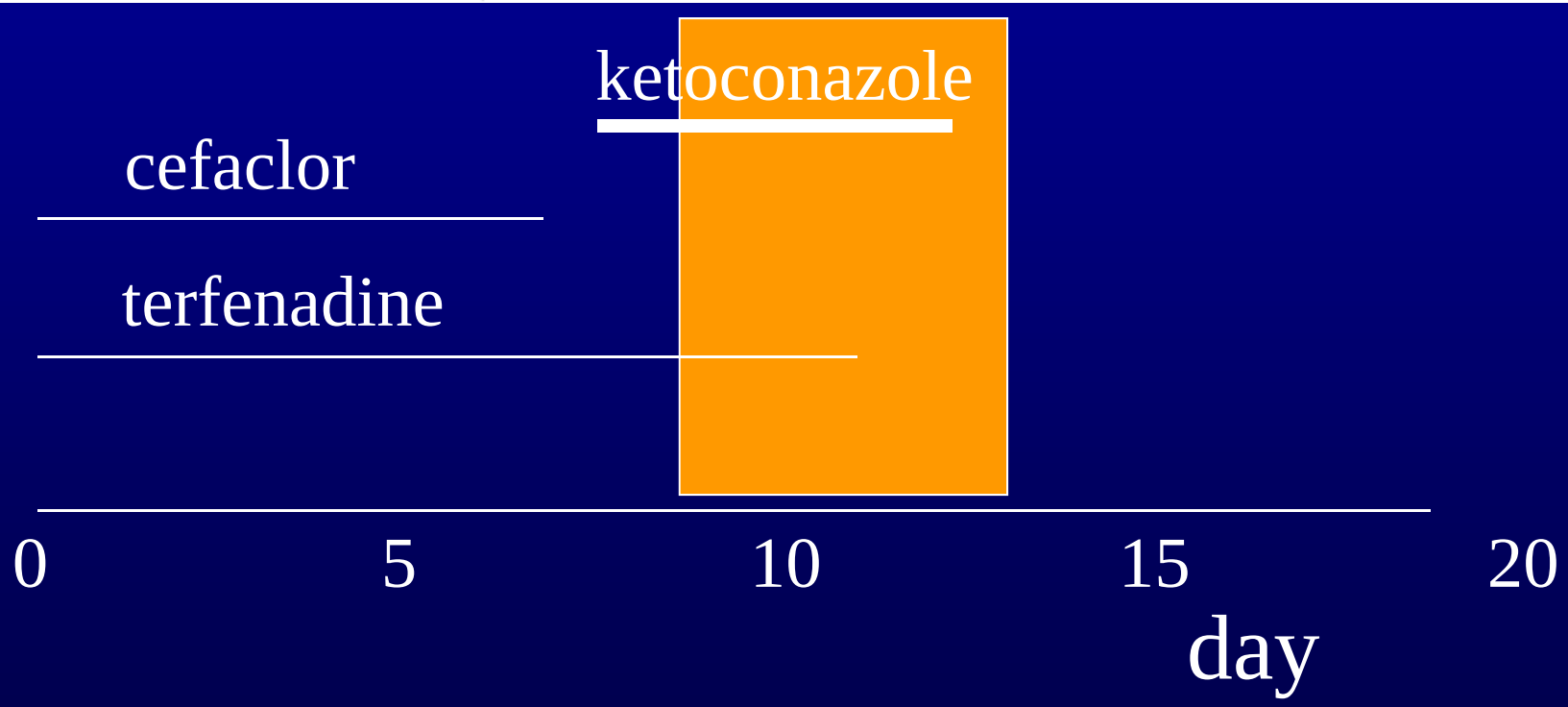
- 39 yo woman
- CC: multiple episodes of syncope with palpitations
- no seizures or syncope in past
- recent sinusitis
  - treated with cefaclor and terfenadine
- subsequent vaginal candidiasis
  - treated with ketoconazole

JAMA 1990

Case Study

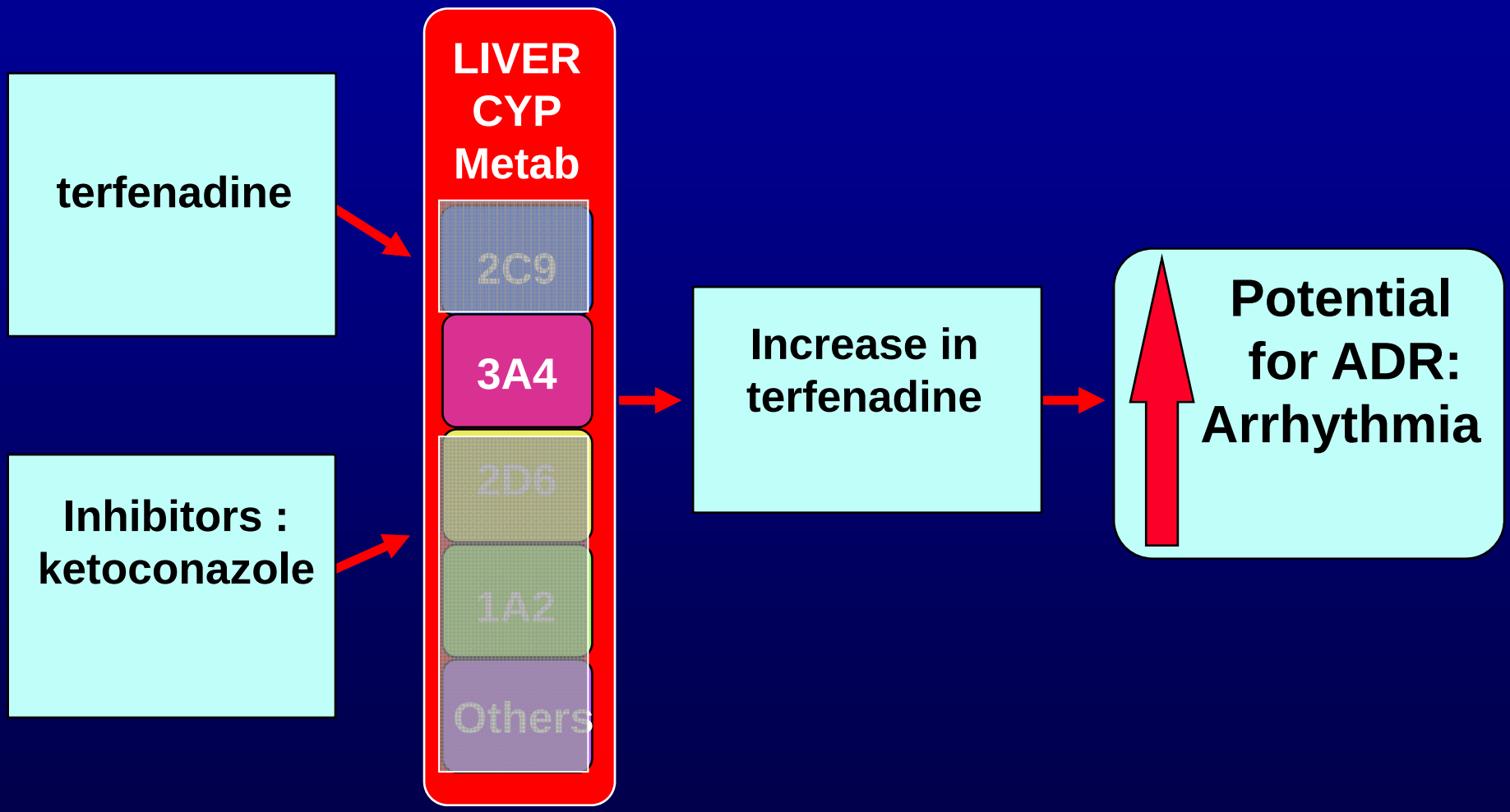
Torsades de pointes





JAMA 1990

Cytochrome P450 Interaction



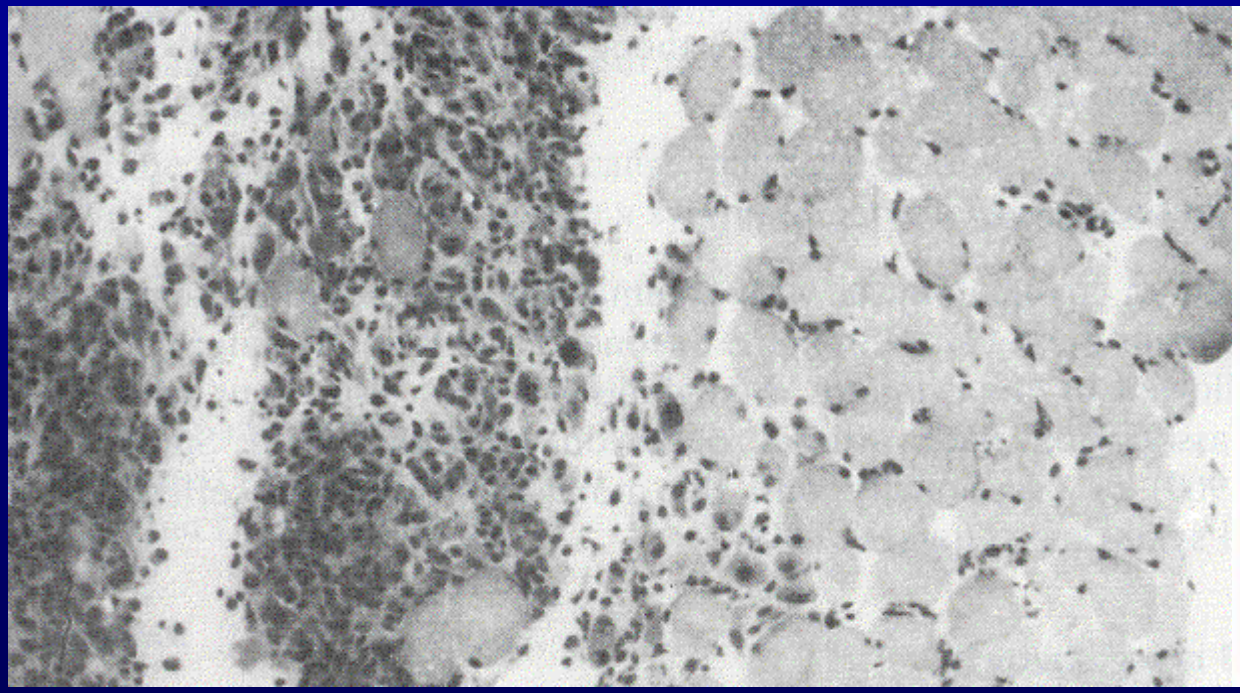
CYP3A4

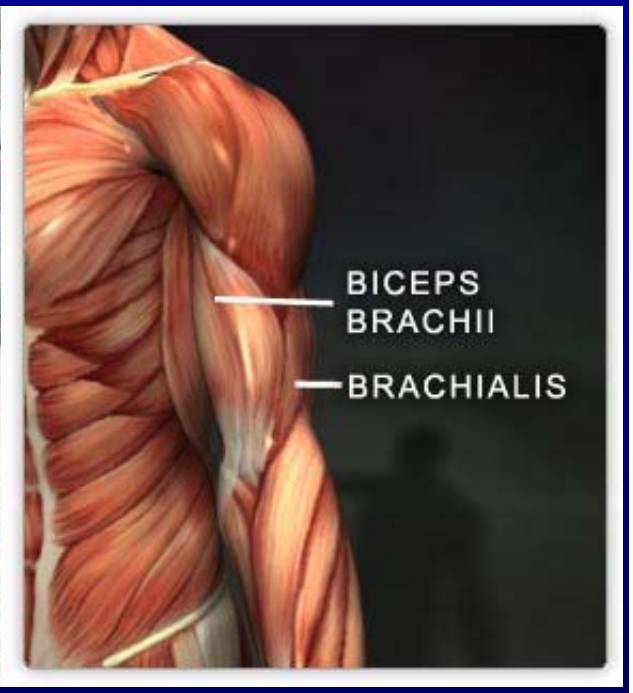
- Most abundant of all P450s in the liver and gut
- Many important substrates (50% of all drugs)
- Inducers: barbiturates, phenytoin, rifampin
- Inhibitors: antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), CCBs, SSRIs, cyclosporine, omeprazole, midazolam & grapefruit juice

Case: Painful workout

- 44 yo man
- Post heart transplant
- ASA
- Simvastatin
- Ramipril
- Sirolimus
- Recent fungal infection – Rx: itraconazole
- Muscle aches and pains – interfering with rehab / exercise

Painful workout

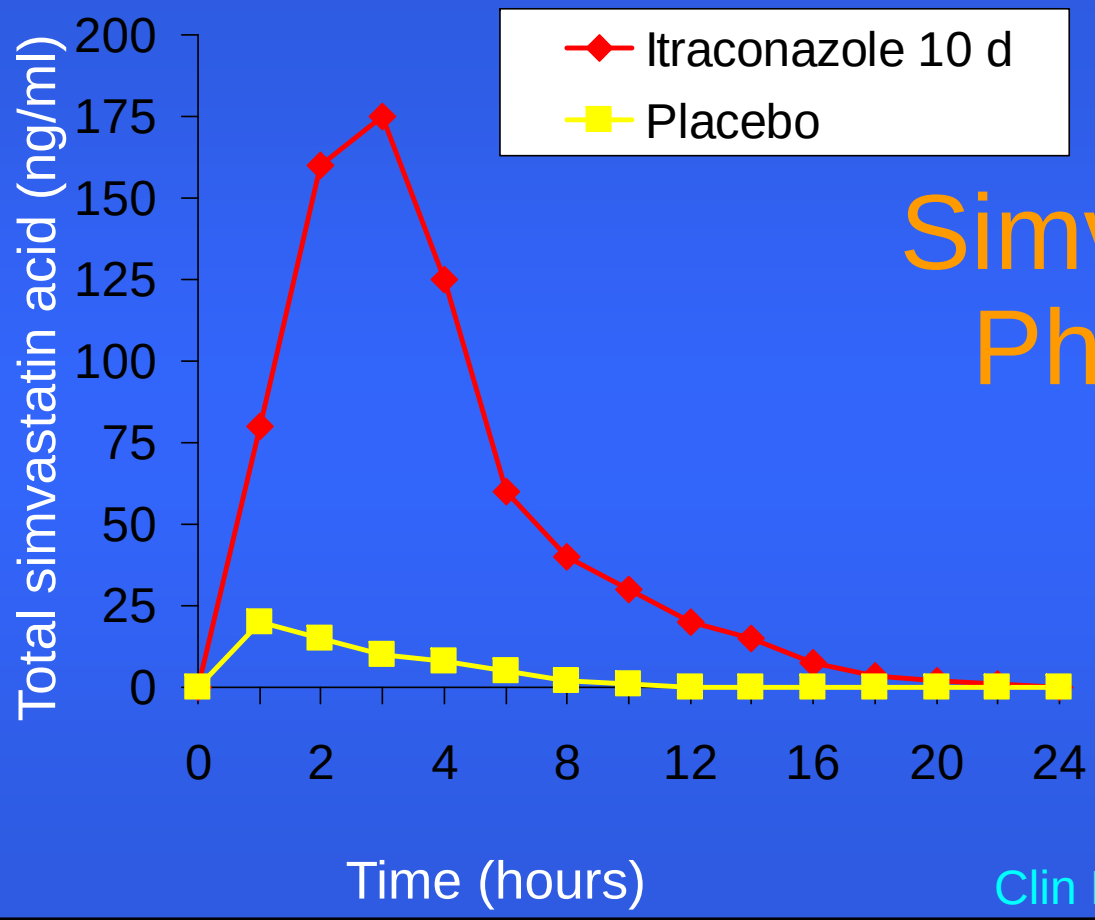




inflamed normal

Interaction Between Itraconazole and Simvastatin

(3A4 inhibitor) (3A4 substrate)

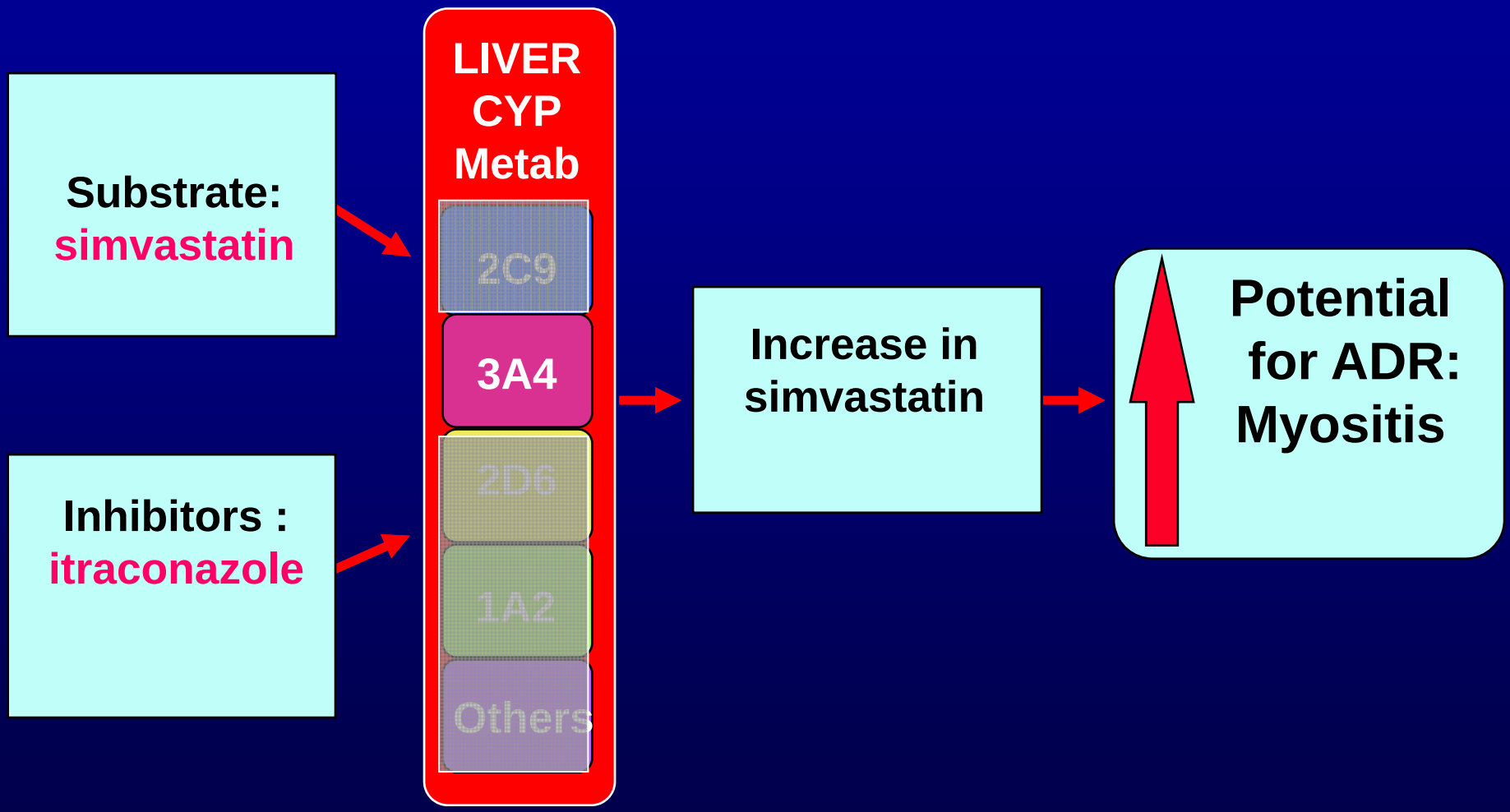


Simvastatin Pharmacokinetics

- **C max 17 x**
- **AUC 19 x**
- **$t_{½}$ 25%**

Clin Pharmacol Ther 1998; 63: 332 - 41

Cytochrome P450 Interaction



Effects of Grapefruit Juice on Simvastatin† Plasma Concentrations

Also for:
- lovastatin
- atorvastatin

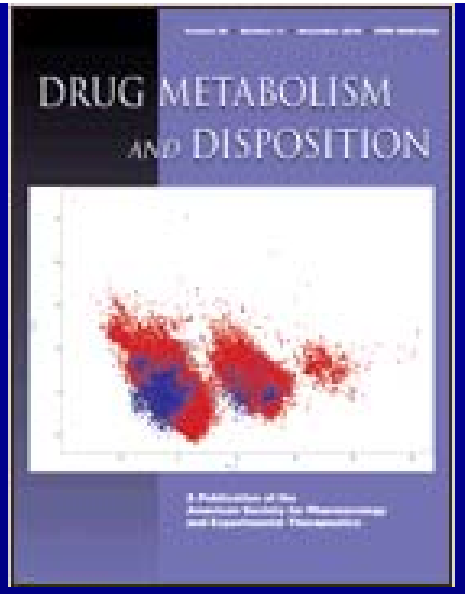
† 40 mg dose

* 200 ml 2x strength grapefruit juice tid for 2 days

** simvastatin administered 24 hours after last dose of grapefruit juice in above regimen

Lilja et al. Clin Pharm Ther. 2000;68: 384

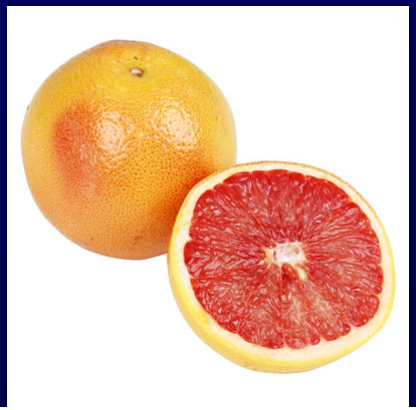
DRUG METABOLISM & DISPOSITION



Identification of 6',7'-dihydroxybergamottin, a cytochrome P450 inhibitor, in grapefruit juice.

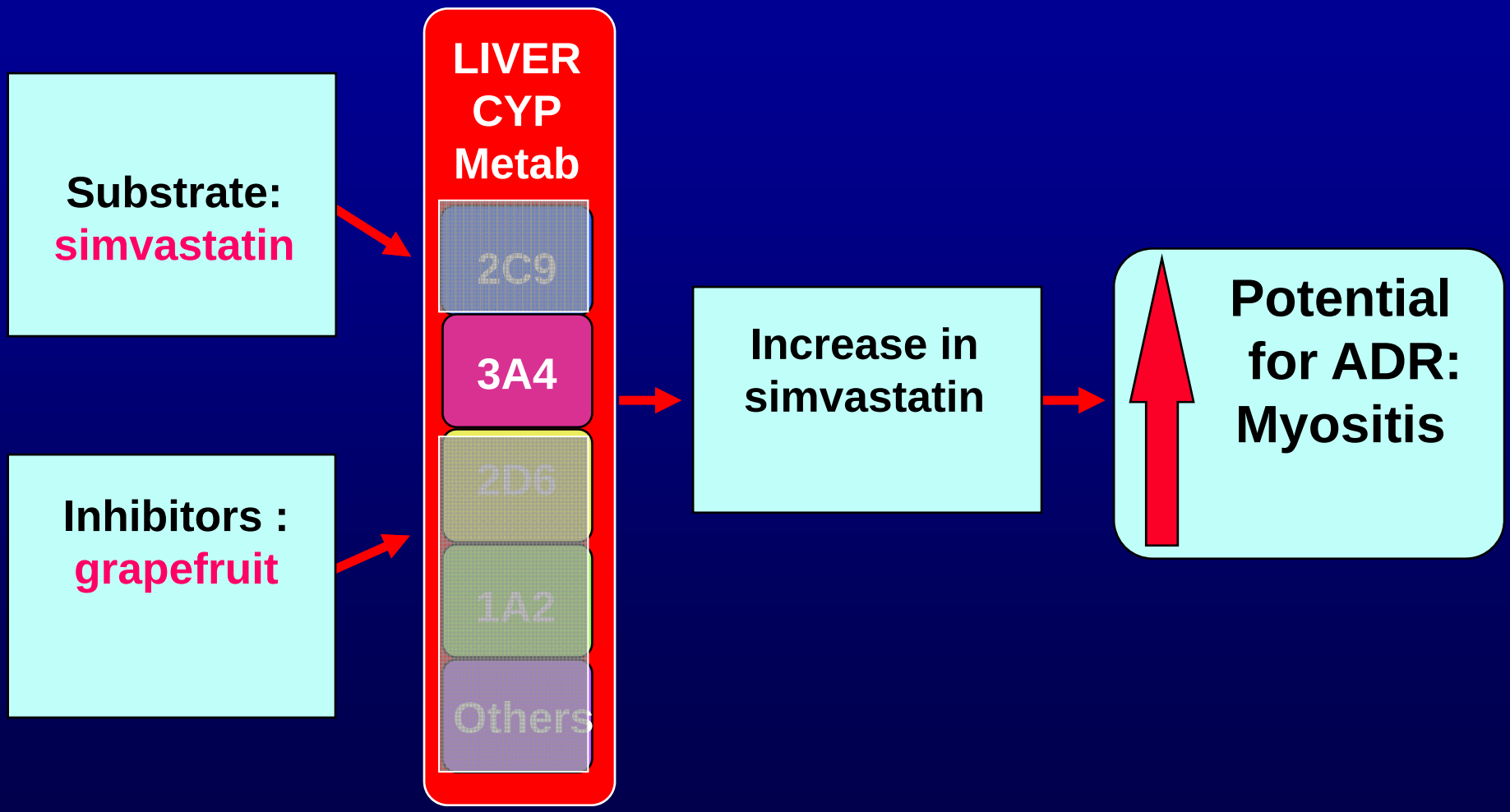
D J Edwards, F H Bellevue, 3rd and P M Woster

DECEMBER 1996 VOL. 24 NO. 12 1287-1290



Seville orange

Cytochrome P450 Interaction

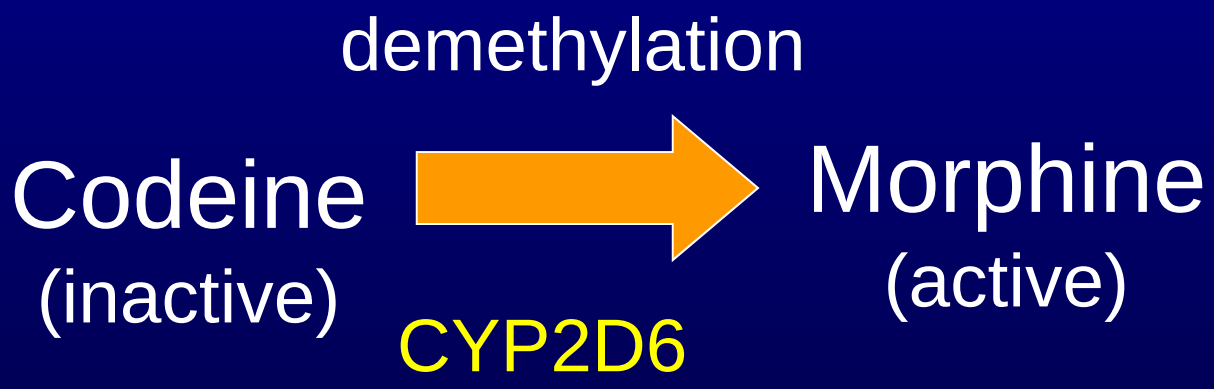


CYP 2D6 Genetics/Anthropology

- genetic diversity in CYP2D6
- drugs using this enzyme pathway (e.g., SSRIs, β-blockers, opiates)
- 3 groups in population
  - Poor metabolizers (PM)
  - Extensive metabolizers (EM) = NORMAL
  - Ultrarapid metabolizers (UM)
- PMs
  - Europeans, White Americans PM = 7.5%
  - Asians, Black Americans PM < 2%

Genetic Polymorphism of metabolizing enzymes

A 2D6 story….



A 2D6 Story

- New mother given standard dose of Tylenol #3 for post-episiotomy pain
- Complained of significant drowsiness and constipation
- Breast fed Infant – poor feeding
- Infant died

2D6 Story

- Mom's serum – high morphine
- Breast milk – high morphine
- Baby's blood – high morphine
- Mom found to have variant 2D6 (ultrarapid) – 2x higher conversion of codeine to morphine – affects 1.4% of population

Smoking, SCTs and Interactions

Smoking and Cytochromes

- Polycyclic aromatic hydrocarbons (PAHs) -- products of incomplete combustion -- are some of the major lung carcinogens found in tobacco smoke.
- PAHs are also potent inducers of the hepatic cytochrome P-450 (CYP) isoenzymes 1A1, **1A2**, and, possibly, 2E1.
- Many drugs are substrates for hepatic CYP1A2, and their metabolism can be induced in smokers, resulting in a clinically significant decrease in pharmacologic effects. Thus, smokers may require higher doses of drugs that are CYP1A2 substrates.

Clin Pharmacokinet. 1999; 36:425-38
Prev Med. 1997; 26:427-34

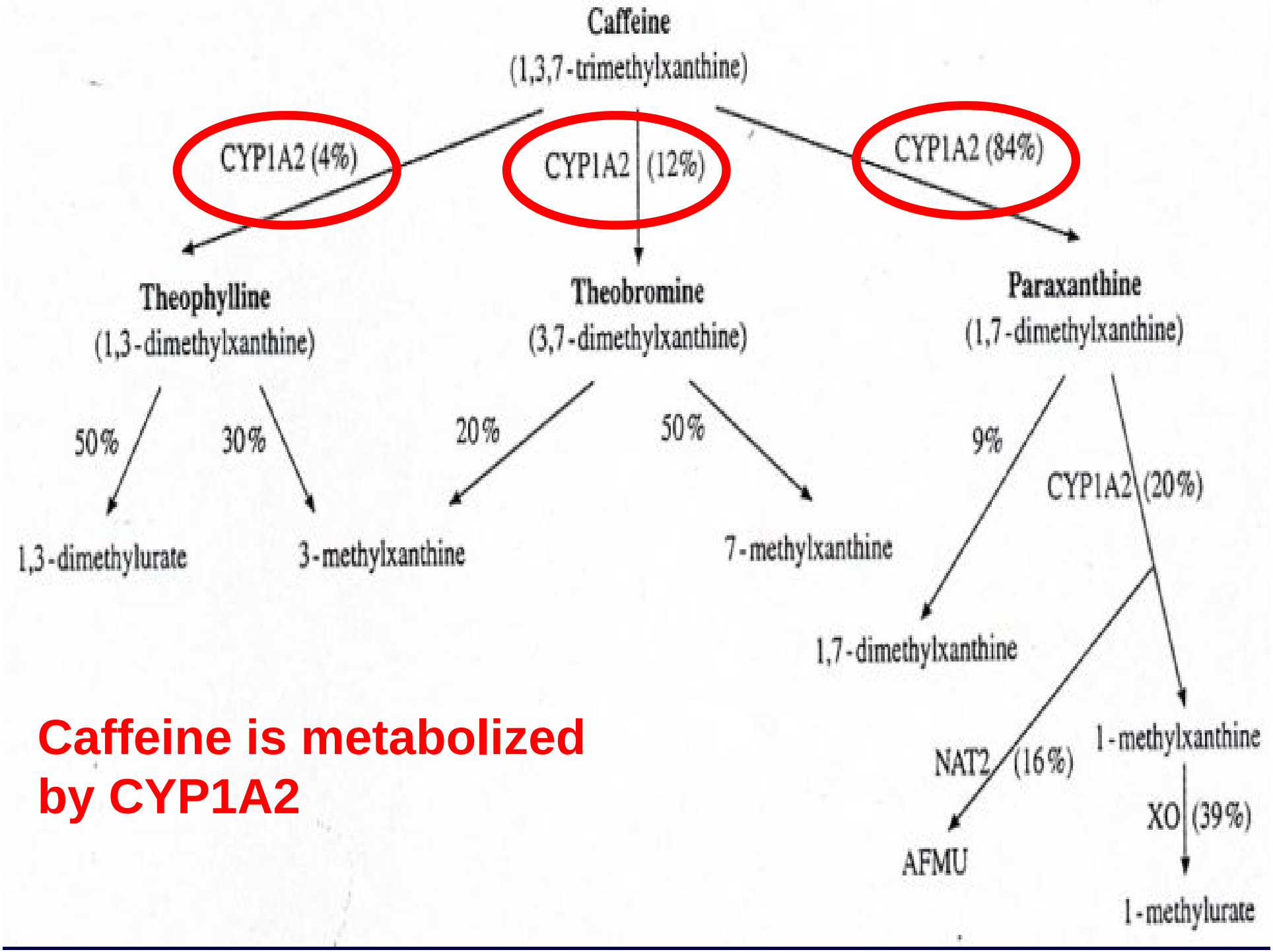
Drug Interaction after Smoking Cessation

- After a person quits smoking, the induction of CYP1A2 dissipates. This is particularly important when a patient is hospitalized and abruptly quits smoking.
- CYP1A2 activity falls to half by ~40hrs after quitting

Clin Pharmacol Ther 2004;76:178-84

Case: The Smoking Gun

- If smoking is so bad….why do I feel worse ***after*** quitting?



Caffeine is metabolized by CYP1A2

Caffeine and Smoking

- Caffeine is >99% metabolized by CYP1A2
- Clearance is increased by 56% in smokers.
- Median caffeine concentrations are twofold to threefold higher in nonsmokers.
- When a patient quits smoking, the patient's caffeine intake should be reduced by half to avoid excessive caffeine levels.
- Symptoms of caffeine toxicity can mimic those of nicotine withdrawal

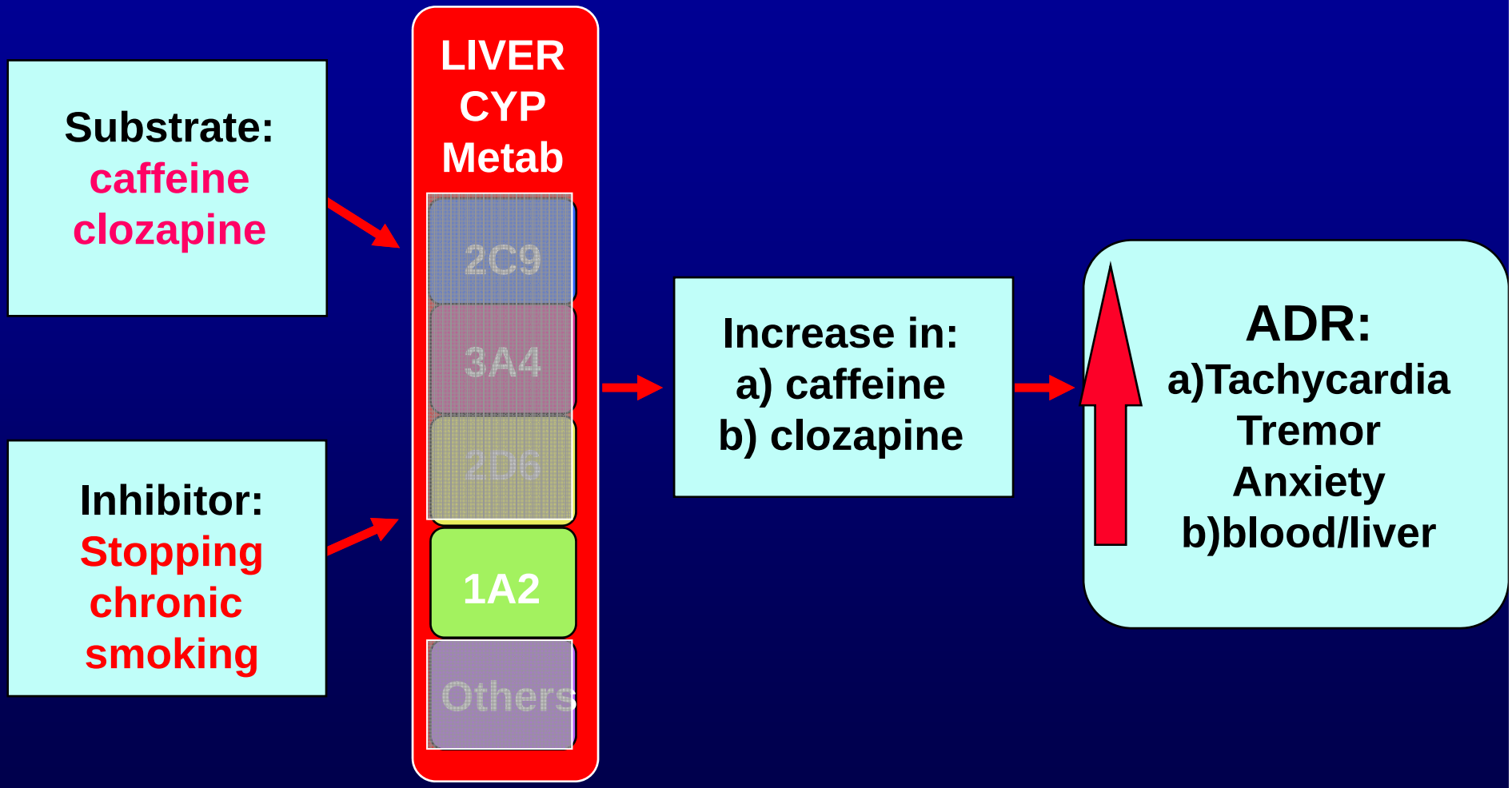
Clin Pharmacokinet 1999; 36:425-38.

Clozapine and Smoking

- clozapine, an atypical antipsychotic drug with a narrow therapeutic range, is metabolized primarily by CYP1A2
- clozapine levels of smokers are much lower than nonsmokers
- when smokers quit, clozapine levels can rise dangerously if not adjusted

J Clin Psychopharmacol. 2001; 21:398-407

Cytochrome P450 Interaction



Case: Seizures Due To Smoking Cessation?

- 35 yr old male
- Chronic schizophrenia
- Stable (7 years Clozapine 700-725mg)
- Sudden onset tonic clonic seizures, coma ICU admission
- Full recovery within 2 days

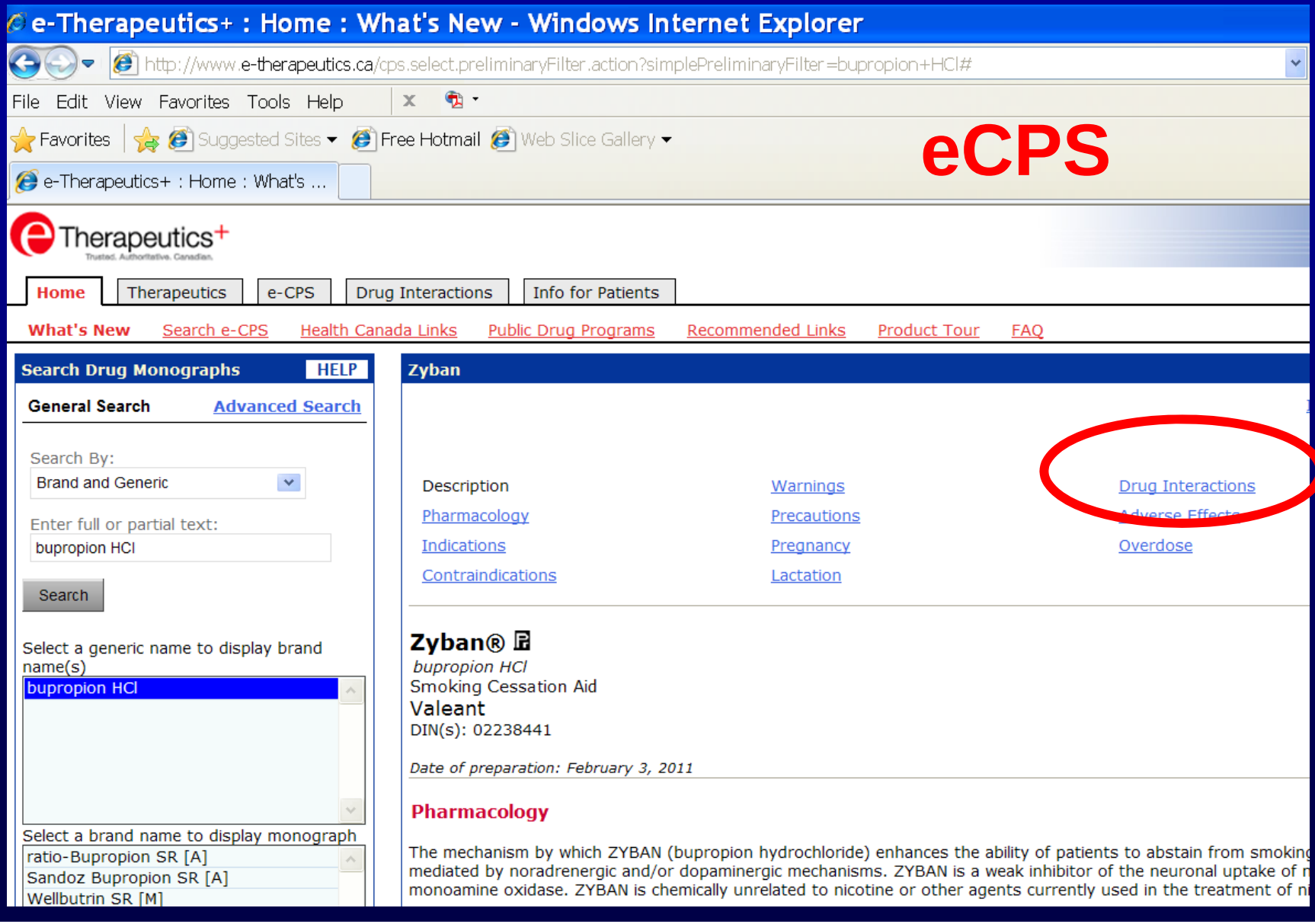
Case: Seizures Due To Smoking Cessation?

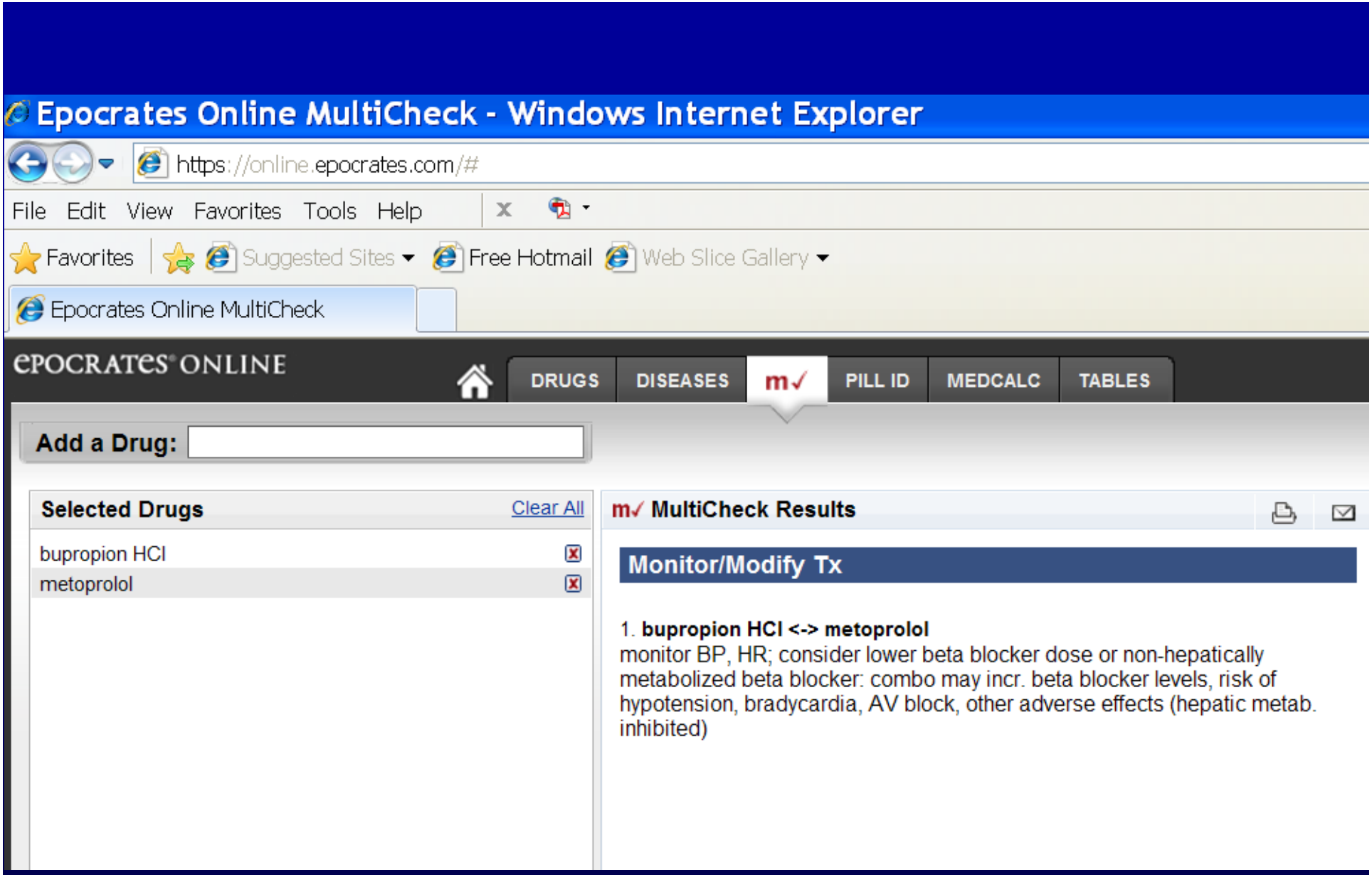
- Abrupt cessation of heavy smoking 2 weeks prior
- After recovery, Clozapine stabilized at 425mg (40% reduction)
- Likely cause is loss of CYP 1A2 induction caused by smoking resulting in plasma level rise of clozapine

Case: Slowing Down

- 70 year old woman
- Post MI – Rx ASA, metoprolol, statin, ACE-I
- Smoking still and depressed – started on bupropion
- Feeling really “slow”
- HR 42

SCTs and Interactions





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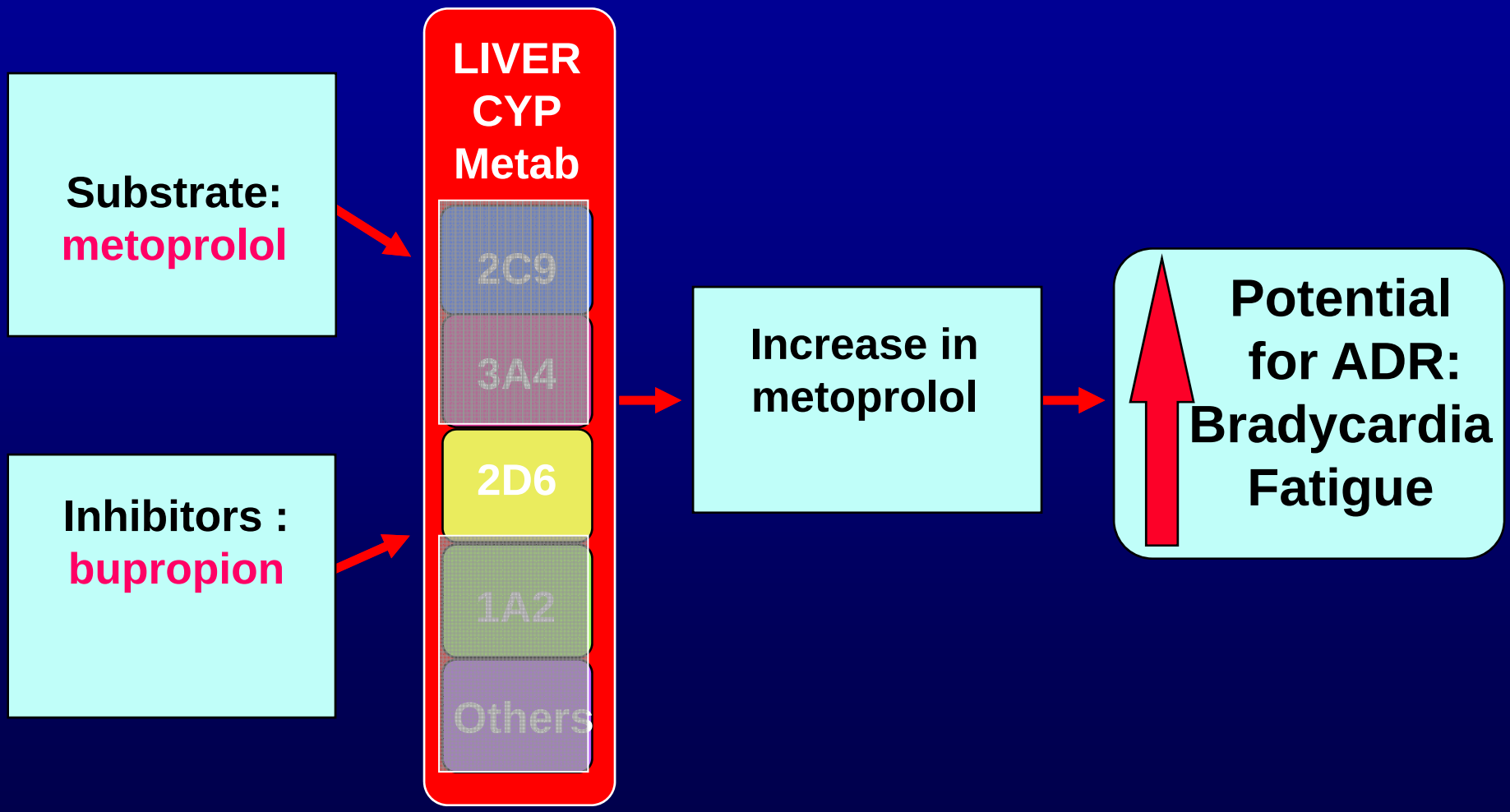
Cytochrome P450 Interaction



SCTs - Varenicline

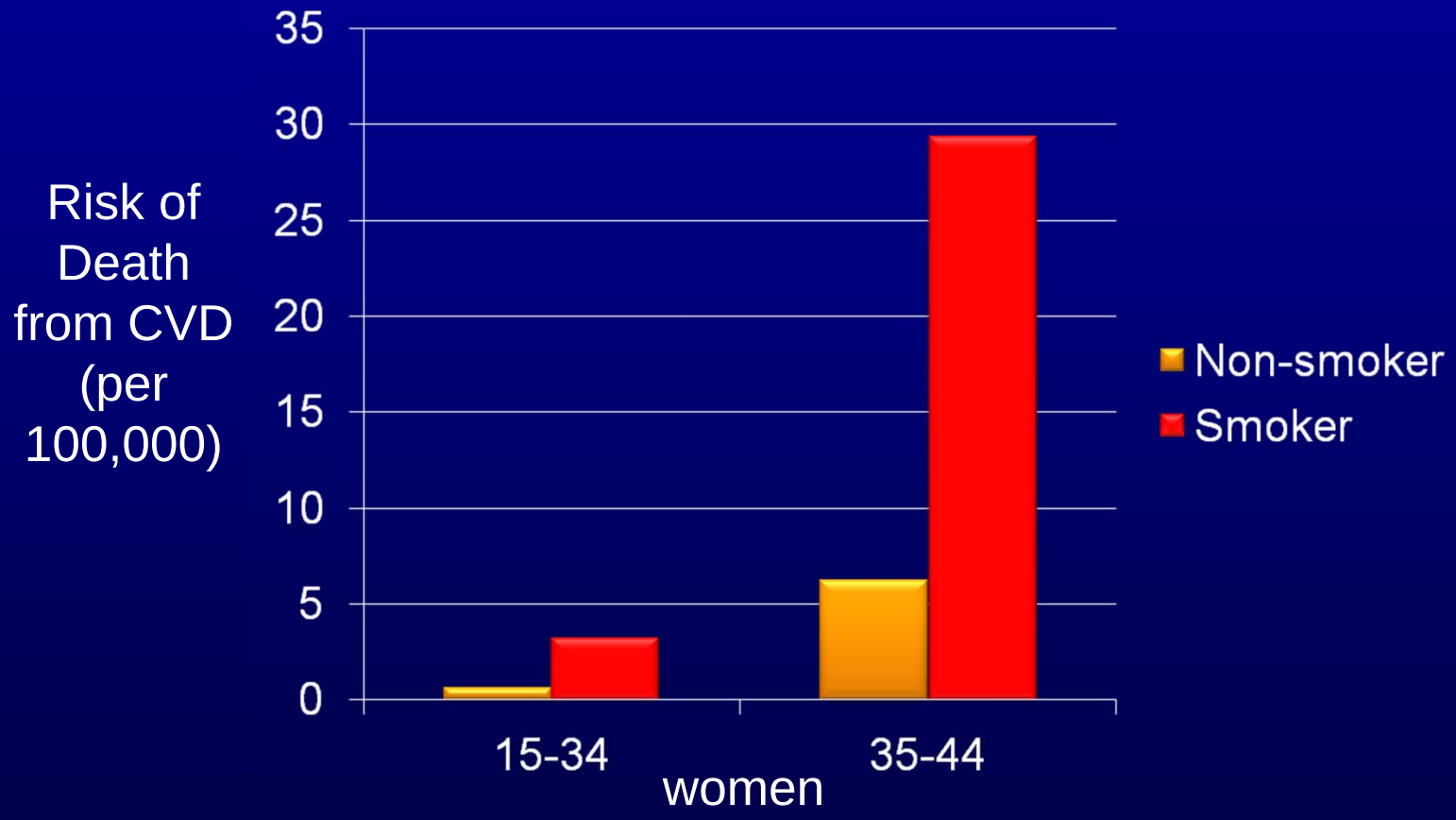
- Minimal metabolism; cleared via kidney
- “Based on varenicline pharmacokinetic characteristics, and clinical experience to date, it appears unlikely that CHAMPIX would produce or be subject to clinically meaningful drug interactions.”
- If co-administered with NRT: “vomiting, dizziness, dyspepsia and fatigue were greater for the combination of varenicline and NRT than for NRT alone”

Pharmaco*dynamic* Interactions

- Smoking in asthma
  - Less benefit from inhaled steroid
- Nicotine and beta-blockers
  - Greater residual sympathetic activation (higher heart rate and BP)

Prev Med. 1997; 26:412-7
Thorax. 2002; 57:226-30

Pharmacodynamic Interactions: Smoking and Oral Contraceptives



Am J Obstet Gynecol. 1999; 180(1, pt. 1):241-9.

Rx for Change

DRUG INTERACTIONS WITH SMOKING

Many interactions between tobacco smoke and medications have been identified. Note that in most cases it is the tobacco smoke—not the nicotine—that causes these drug interactions. Tobacco smoke may interact with medications through pharmacokinetic (PK) or pharmacodynamic (PD) mechanisms. PK interactions affect the absorption, distribution, metabolism, or elimination of other drugs, potentially causing an altered pharmacologic response. The majority of PK interactions with smoking are the result of induction of hepatic cytochrome P450 enzymes (primarily CYP1A2). PD interactions alter the expected response or actions of other drugs. The amount of tobacco smoking needed to have an effect has not been established and the assumption is that any smoker is susceptible to the same degree of interaction. The most clinically significant interactions are depicted in the shaded rows.

DRUG/CLASS	MECHANISM OF INTERACTION AND EFFECTS
Pharmacokinetic Interactions	
Alprazolam (Xanax)	▪ Conflicting data on significance of a PK interaction. Possible ↓ plasma concentrations (up to 50%); ↓ half-life (35%).
Caffeine	▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (56%). ▪ Likely ↑ caffeine levels after cessation.
Chlorpromazine (Thorazine)	▪ ↓ Area under the curve (AUC) (36%) and serum concentrations (24%). ▪ ↓ Sedation and hypotension possible in smokers; smokers may need ↑ dosages.
Clozapine (Clozaril)	▪ ↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (18%).
Flecainide (Tambocor)	▪ ↑ Clearance (61%); ↓ trough serum concentrations (25%). ▪ Smokers may need ↑ dosages.
Fluvoxamine (Luvox)	▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (24%); ↓ AUC (31%); ↓ plasma concentrations (32%). ▪ Dosage modifications not routinely recommended but smokers may need ↑ dosages.
Haloperidol (Haldol)	▪ ↑ Clearance (44%); ↓ serum concentrations (70%).
Heparin	▪ Mechanism unknown but ↑ clearance and ↓ half-life are observed. Smoking has prothrombotic effects. ▪ Smokers may need ↑ dosages due to PK and PD interactions.
Insulin, subcutaneous	▪ Possible ↓ insulin absorption secondary to peripheral vasoconstriction; smoking may cause release of endogenous substances that cause insulin resistance. ▪ PK & PD interactions likely not clinically significant; smokers may need ↑ dosages.
Insulin, inhaled (Exubera)	▪ Systemic exposure is greatly increased in smokers; greater maximal insulin concentrations (3–5 fold) and faster (by 20-30 minutes) ; ↑AUC 2–3 fold ▪ Contraindicated in smokers and those who have discontinued smoking for less than 6 months.
Mexiletine (Mexitil)	▪ ↑ Clearance (25%; via oxidation and glucuronidation); ↓ half-life (36%).
Olanzapine (Zyprexa)	▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (98%); ↓ serum concentrations (12%). ▪ Dosage modifications not routinely recommended but smokers may require ↑ dosages.
Propranolol (Inderal)	▪ ↑ Clearance (77%; via side chain oxidation and glucuronidation)
Tacrine (Cognex)	▪ ↑ Metabolism (induction of CYP1A2); ↓ half-life (50%); serum concentrations three-fold lower. ▪ Smokers may need ↑ dosages.
Theophylline (Theo Dur, etc.)	▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (58–100%); ↓ half-life (63%). ▪ Levels should be monitored if smoking is initiated, discontinued, or changed. ▪ ↑ Clearance with second-hand smoke exposure. ▪ Maintenance doses are considerably higher in smokers.
Tricyclic antidepressants (e.g., imipramine, nortriptyline)	▪ Possible interaction with tricyclic antidepressants in the direction of ↓ blood levels, but the clinical importance is not established.
Pharmacodynamic Interactions	
Benzodiazepines (diazepam, chlordiazepoxide)	▪ ↓ Sedation and drowsiness, possibly caused by nicotine stimulation of central nervous system.
Beta-blockers	▪ Less effective antihypertensive and heart rate control effects; might be caused by nicotine-mediated sympathetic activation. ▪ Smokers may need ↑ dosages.
Corticosteroids, inhaled	▪ Asthmatic smokers may have less of a response to inhaled corticosteroids.
Hormonal contraceptives	▪ ↑ Risk of cardiovascular adverse effects (e.g., stroke, myocardial infarction, thromboembolism) in women who smoke and use oral contraceptives. ▪ ↑ Risk with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women age 35 and older.
Opioids (propoxyphene, pentazocine)	▪ ↓ Analgesic effect; smoking may ↑ the metabolism of propoxyphene (15–20%) and pentazocine (40%). Mechanism unknown. ▪ Smokers may need ↑ opioid dosages for pain relief.

Adapted from Zevin S, Benowitz NL. Drug interactions with tobacco smoking. *Clin Pharmacokinet* 1999;36:425–438.

www.medscape.com


UH, DAD... YOU MIGHT WANT TO TALK TO YOUR DOCTOR ABOUT DRUG INTERACTION...
@#$%!
OH, YEAH? %#@$!