Cytochrome P450 (CYP) Enzymes

- Enzyme systems that are responsible for metabolizing most psychotropic medications
- Genetic polymorphism
  - Super Extensive metabolizers (SEM's)
  - Extensive metabolizers (EMs)
  - Poor metabolizers (PMs)
  - Slow metabolizers (SM's)
- Can be induced by specific substrates:
  - phenobarbital, ethanol, and steroids
- Can also be inhibited by various medications that are potent competitive inhibitors of the enzymes:
  - cimetidine and ketoconazole

Richelson 1997; Sjoqvist et al, 1997; Gonzalez 1992; Kalow 1991

*

P450 Enzyme System involved in Psychotropic metabolism

CYP 1A2	Drug metabolism
CYP 2A6	Nicotine metabolism
CYP 2C19	Drug metabolism
CYP 2D6	Drug metabolism
CYP 2E1	Alcohol metabolism
CYP 3A3/4	Drug metabolism

Adapted from Smith 2005

CYP2D6
(Debrisoquin hydroxylase)

- Inter-ethnic differences (+)
  - Whites: 5%-10% are PMs
  - African Americans and Asians: 1%-6% are PM's
    - At least 9 mutant forms of the enzyme
  - 33%-50% of Asian and African EMs are IMs (less active)
    - Polymorphism (+)

Richelson 1997; Sjoqvist et al, 1997; Edeki 1996; Sjoqvist et al, 1997

*

CYP2D6 Substrates

- Antipsychotics-
  haloperidol*, reduced haloperidol, perphenazine, phenothiazines*, thioridazine*, olanzapine*, risperidone*, sertindole*
- Antidepressants-
  amytrptiline*, desipramine, imipramine*, nortryptiline, trazadone, fluoxetine, paroxetine, venlafaxine
- Cardiovascular Agents-
  encanide, flecanide, propanalol*, metropolol, timolol
- Opiates- codeine*, dextramethorphan, hydrocodone*
- galanthamine

Adapted from Smith 2005

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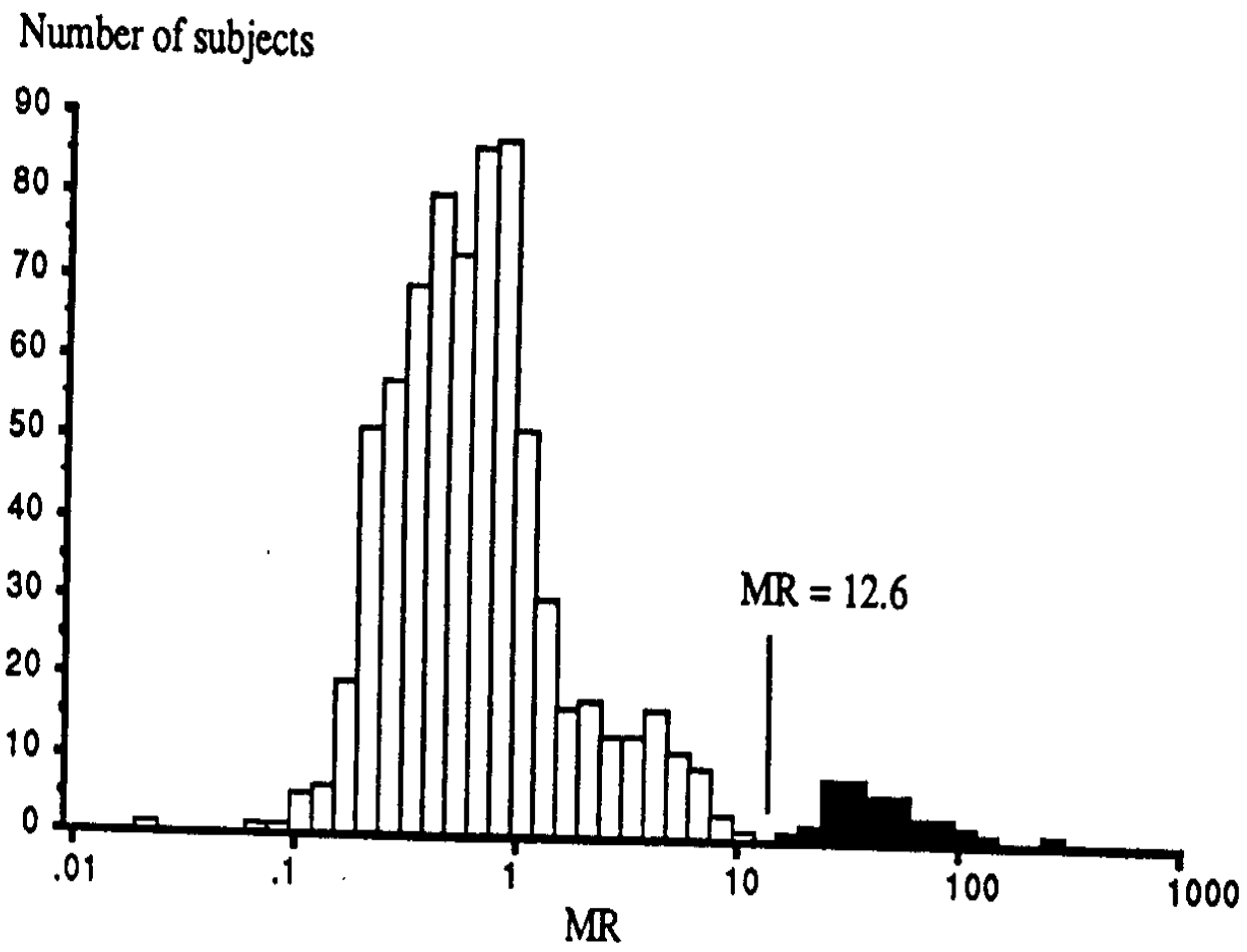
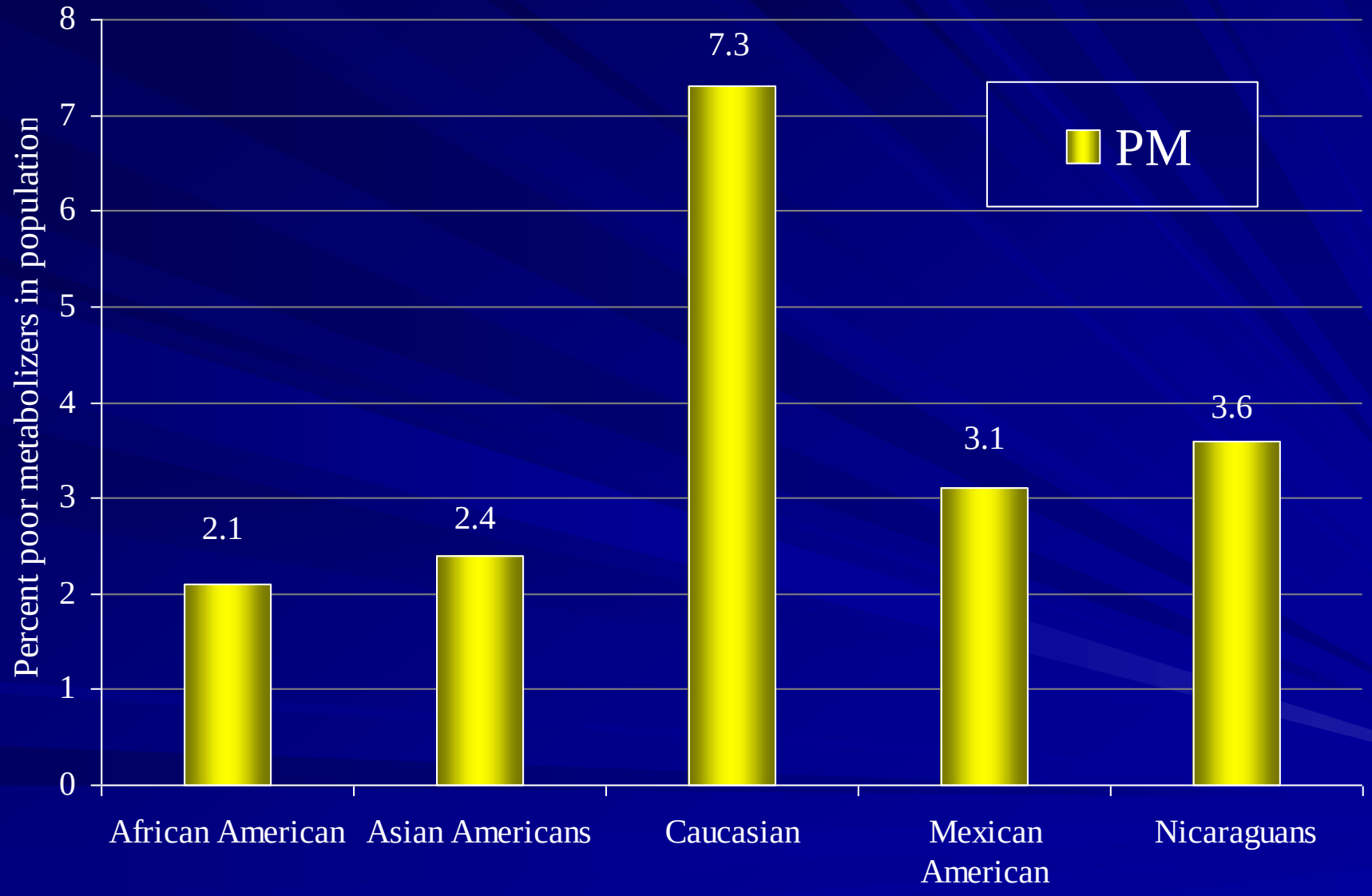
Distribution of CYP2D6 Activity in Caucasian Populations



CYP2D6 Poor Metabolizers



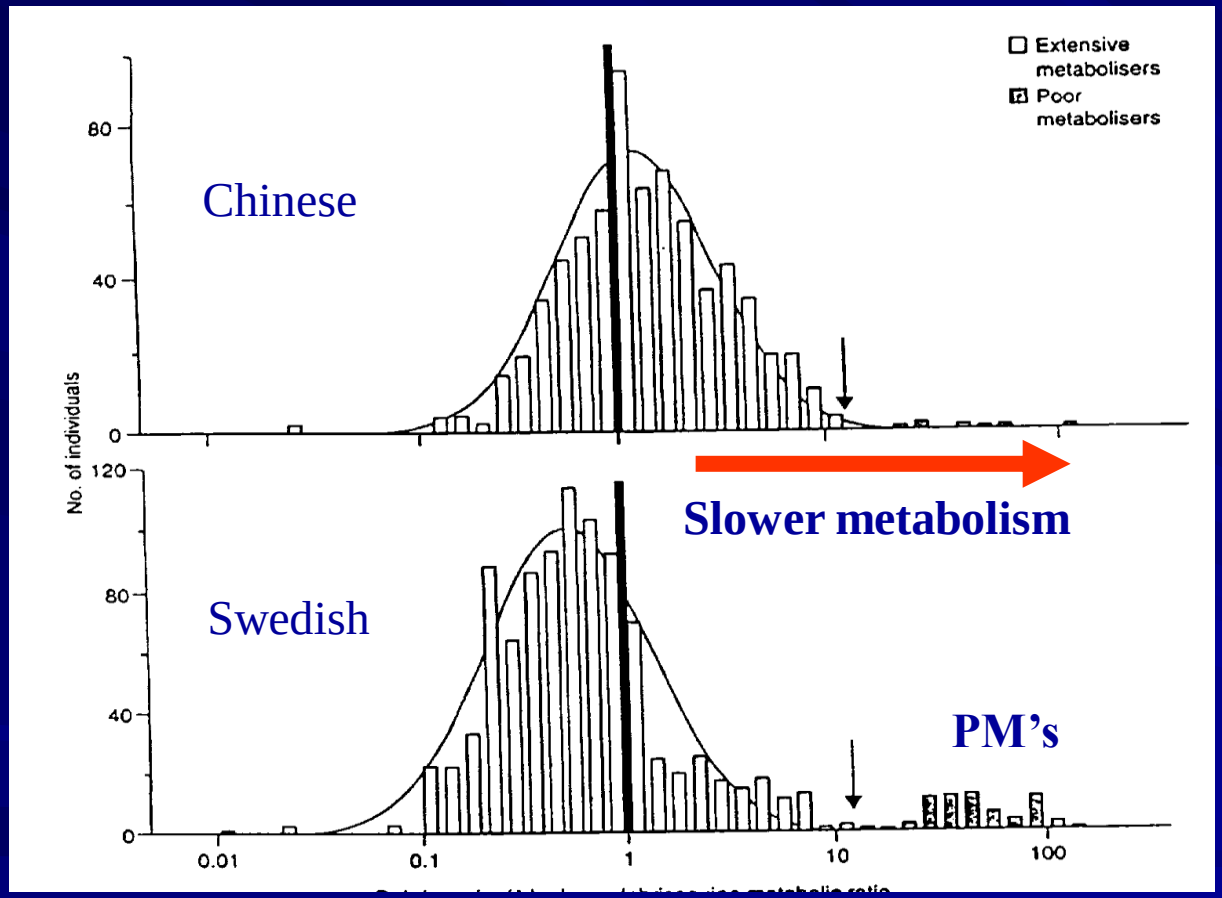
Adapted from Smith 2005

CYP2D6 Metabolic Rates

Metabolic type	**Rate of metabolism**	**Plasma Drug levels**	**Clinical Effects**
PM **Poor metabolizer**	**No metabolism**	Toxic drug levels	Side effects
EM Extensive metabolizer	Normal metabolism	Normal drug level	Normal response

Adapted from Smith 2005

Ethnic Variation in CYP2D6 Activity



Debrisoquine/4-hydroxy-debrisoquine metabolic ratio

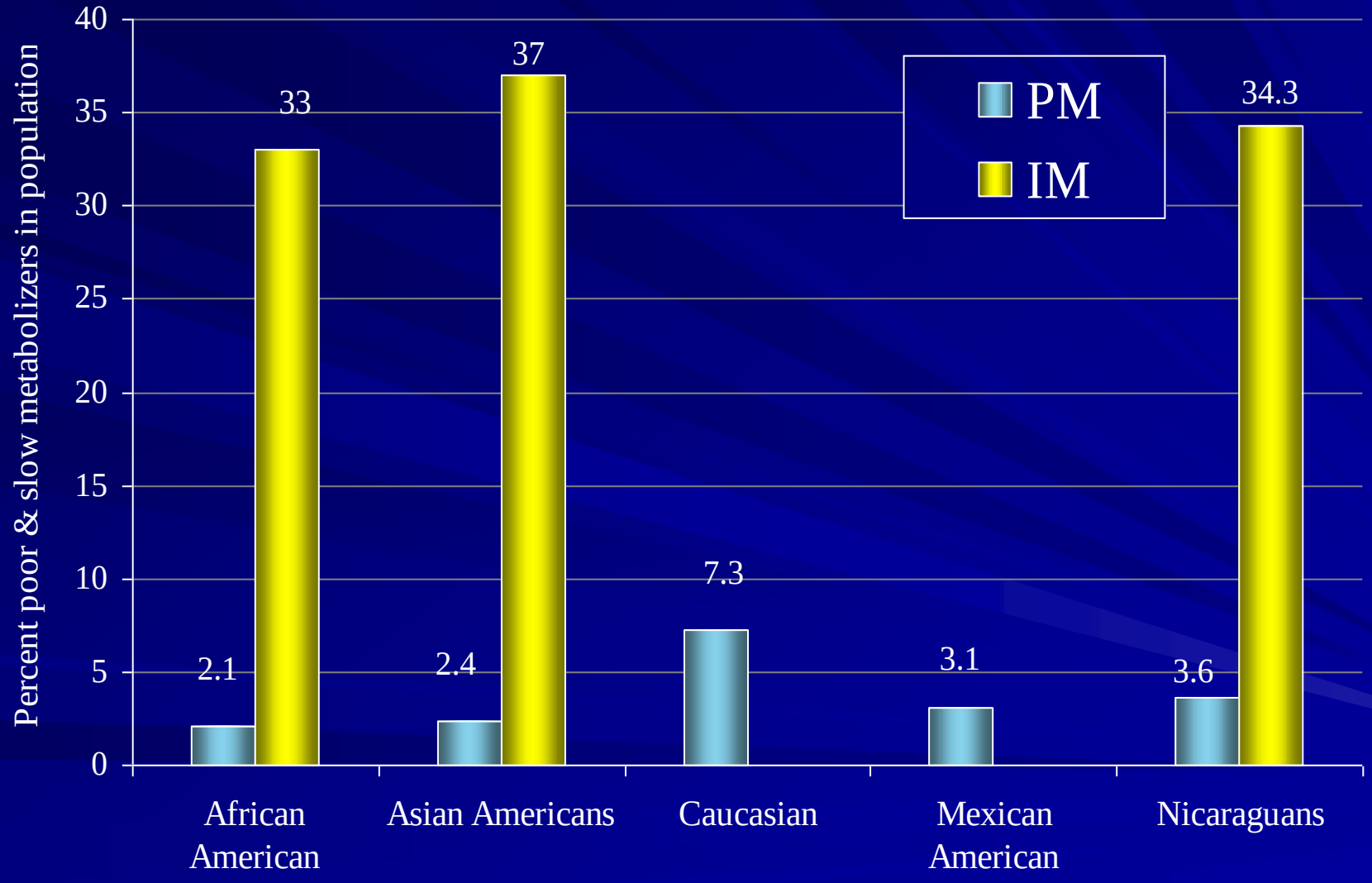
Histograms of CYP2D6 activity in Chinese and Swedish Caucasians display variations in activity. Although Chinese display lower PM rates, they display lower overall metabolic activity due in part to higher rates of IM's

CYP2D6 Metabolic Rates

Metabolic type	Rate of metabolism	Plasma Drug levels	Clinical Effects
IM Intermediate metabolizer	Slow metabolism	High drug levels	Side effects- higher dose
UM Ultra metabolizer	Super fast metabolism	Low or no drug level	No response at normal doses

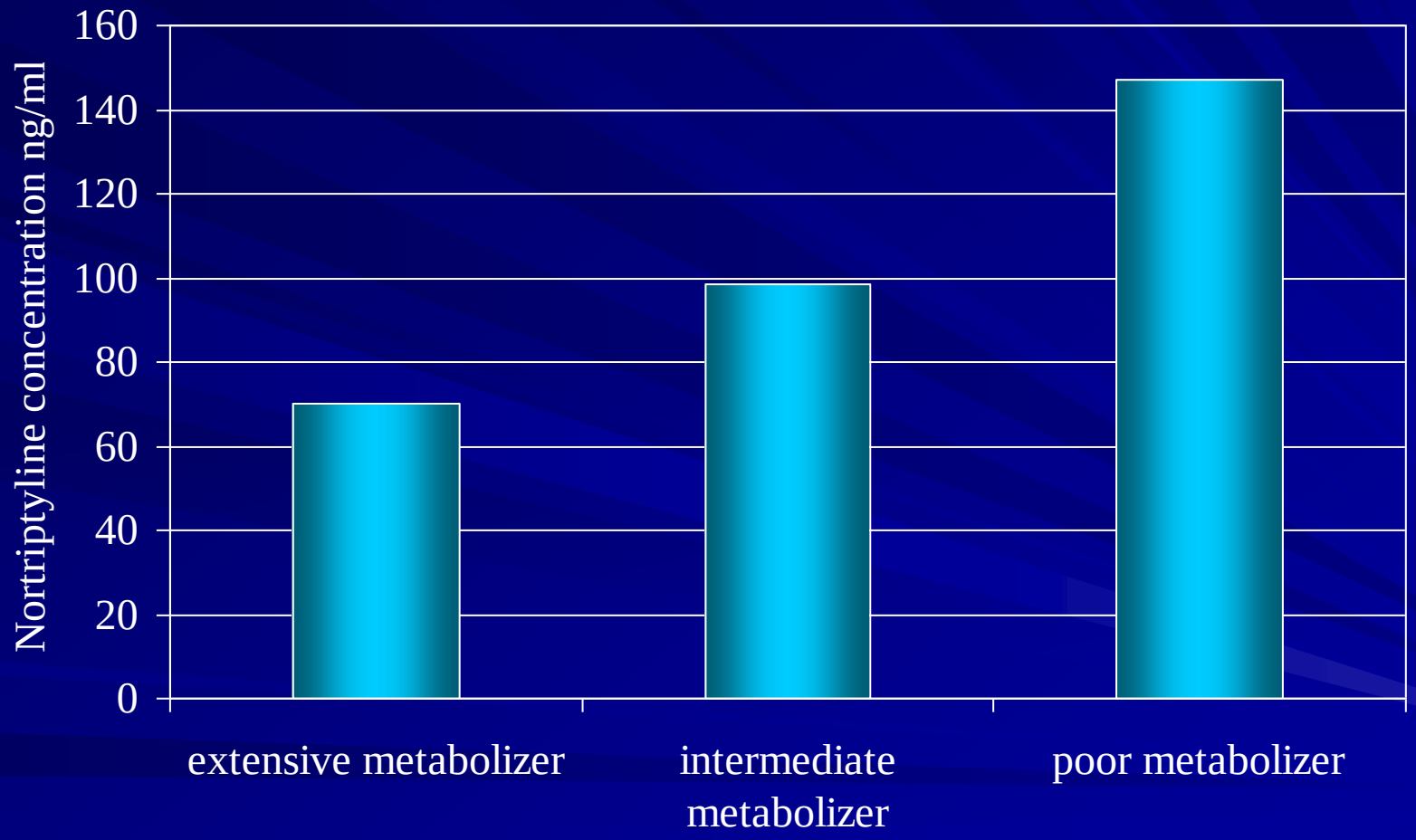
Adapted from Smith 2005

CYP2D6 Poor & Intermediate Metabolizers



adapted from Smith 2005

Nortriptyline Plasma Levels in Japanese: Impact of CYP2D6 phenotype



Morita, et al, 2000

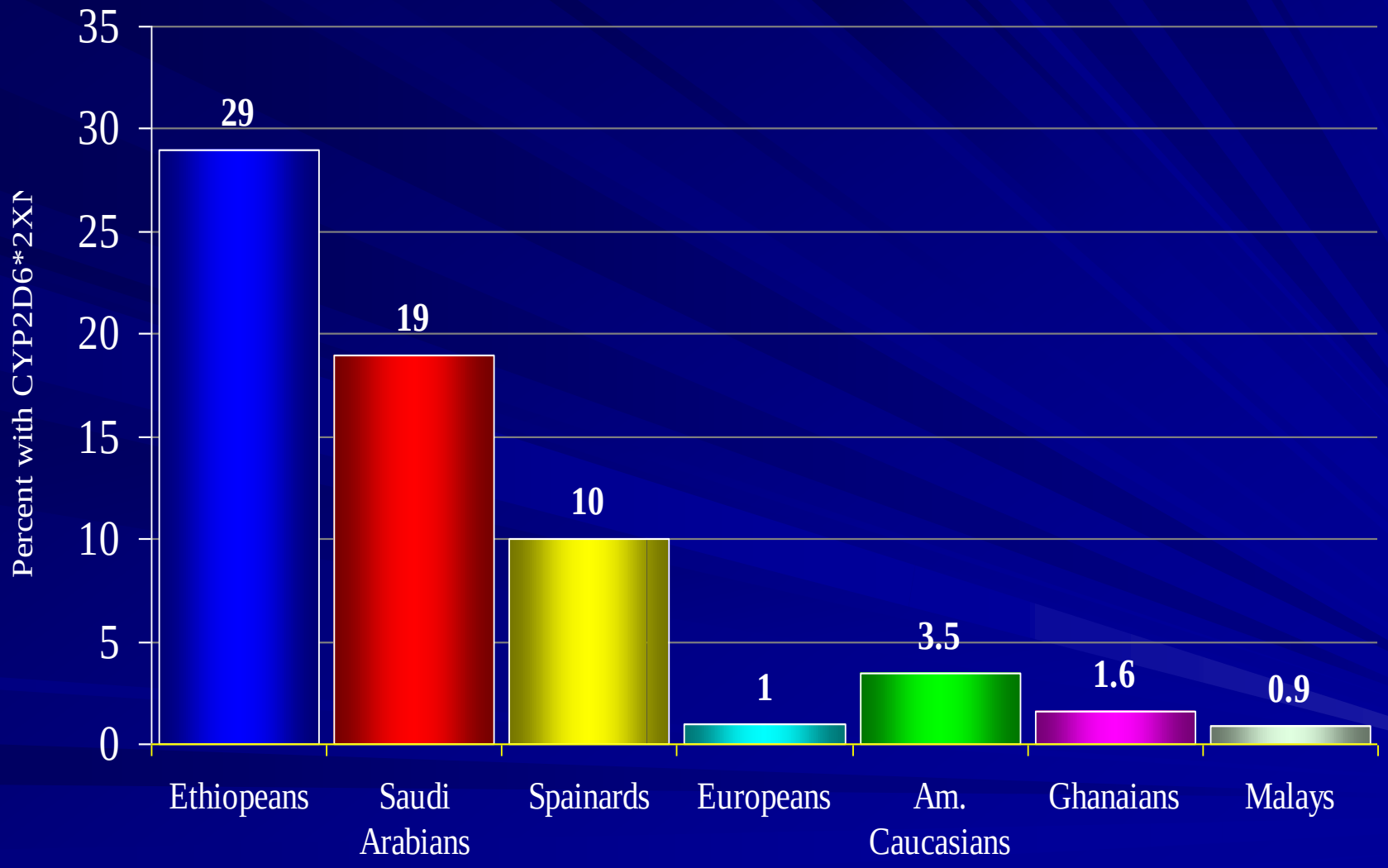
CYP2D6 Inhibitors

- Antidepressants
  - Fluoxetine, paroxetine, moclebemide
- Antipsychotics
  - Haloperidol, fluphenazine, perphenazine, pimozide, thioridazine
- Antihistamines
  - Diphenhydramine, chlorpheniramine, tripelennamine, promethazine, hydroxyzine, clemastine
  - Terfenadine, astemizole, loratadine
- Misc.
  - Cimetidine, methadone, quinidine, ritanovir, celecoxib

Hamelin et al, 1998; Nicolas, et al, 1999; Werner et al, 2003.

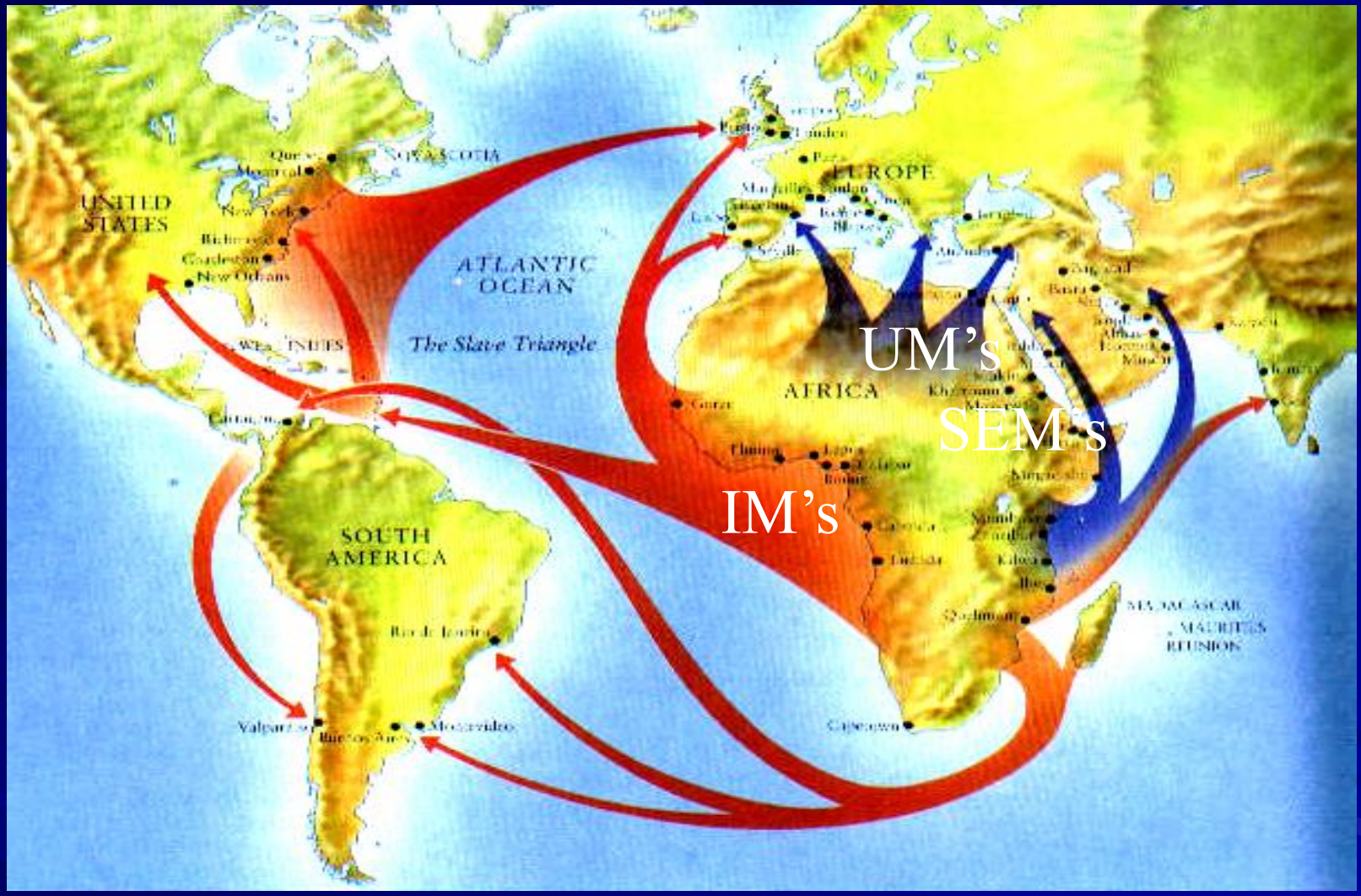
*

CYP2D6 Ultra Metabolizers



Adapted from Smith 2005

Geographic Origin of IM & UM's



The highest frequency of ultra metabolizers (UM's) are found in north east Africa and the Mediterranean area. High frequencies of intermediate metabolizers (IM's) are found in South west Africa and East Asia (not pictured).

adapted from Smith 2005

CYP2D6 Genotypes

Poor Metabolizers (PM) are more likely to have higher rates of:

- EPS
- TD
- venlafaxine cardiovascular toxicity
- longer hospital stay
- intolerant to standard pharmacotherapy
- cost of treatment $4,000 to $6,000 per year greater

Ultra Metabolizers (SEM) are more likely to have higher rates of:

- resistant to standard pharmacotherapy
- frequent hospitalizations
- oral opiate addiction
- > 20 cigarettes/ day
- cost of treatment $4,000 to $6,000 per year greater

Chou, et al, 2000; Zabrocka, et al, 1999; Reggiani, et al, 2000

CYP2C19
(Mephenytoin hydroxylase)

- Inter-ethnic differences (+)
- Polymorphism (+)
- 2%-10% of whites have little or no activity
- 15%-25% of African American and Asians may be PMs
- The enzyme metabolizes diazepam and several antidepressants

Horai et al, 1989; Kupfer and Preisig 1984

*

Drugs Metabolized by CYP2C19

Benzodiazepines

- diazepam

Antidepressants

- imipramine, amitriptyline, clomipramine
- citalopram*, sertraline*

Others

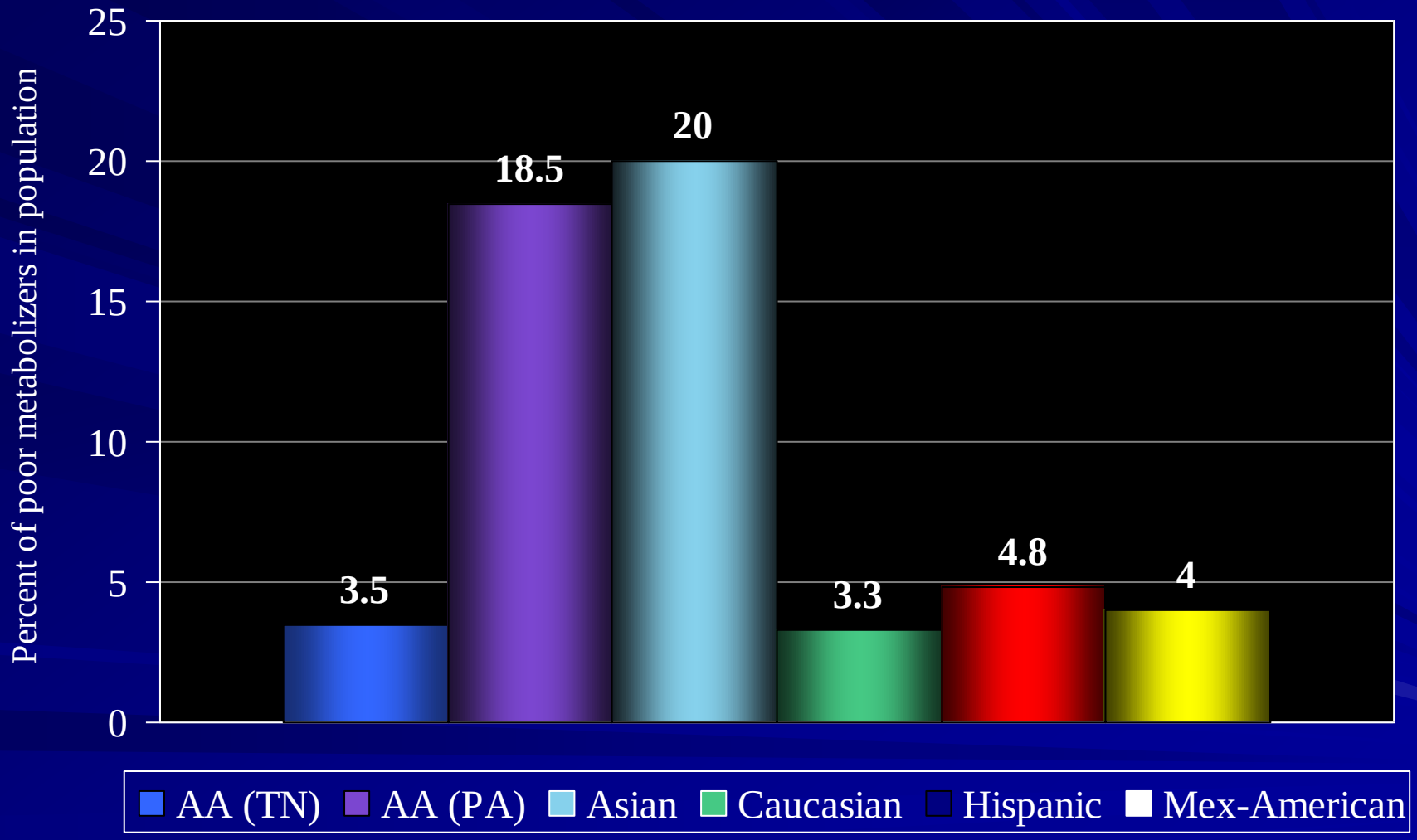
- propranolol, hexobarbital, mephobarbital
- proguanil, omeprazole, S-mephenytoin

*partial route of metabolism

adapted from Smith 2005

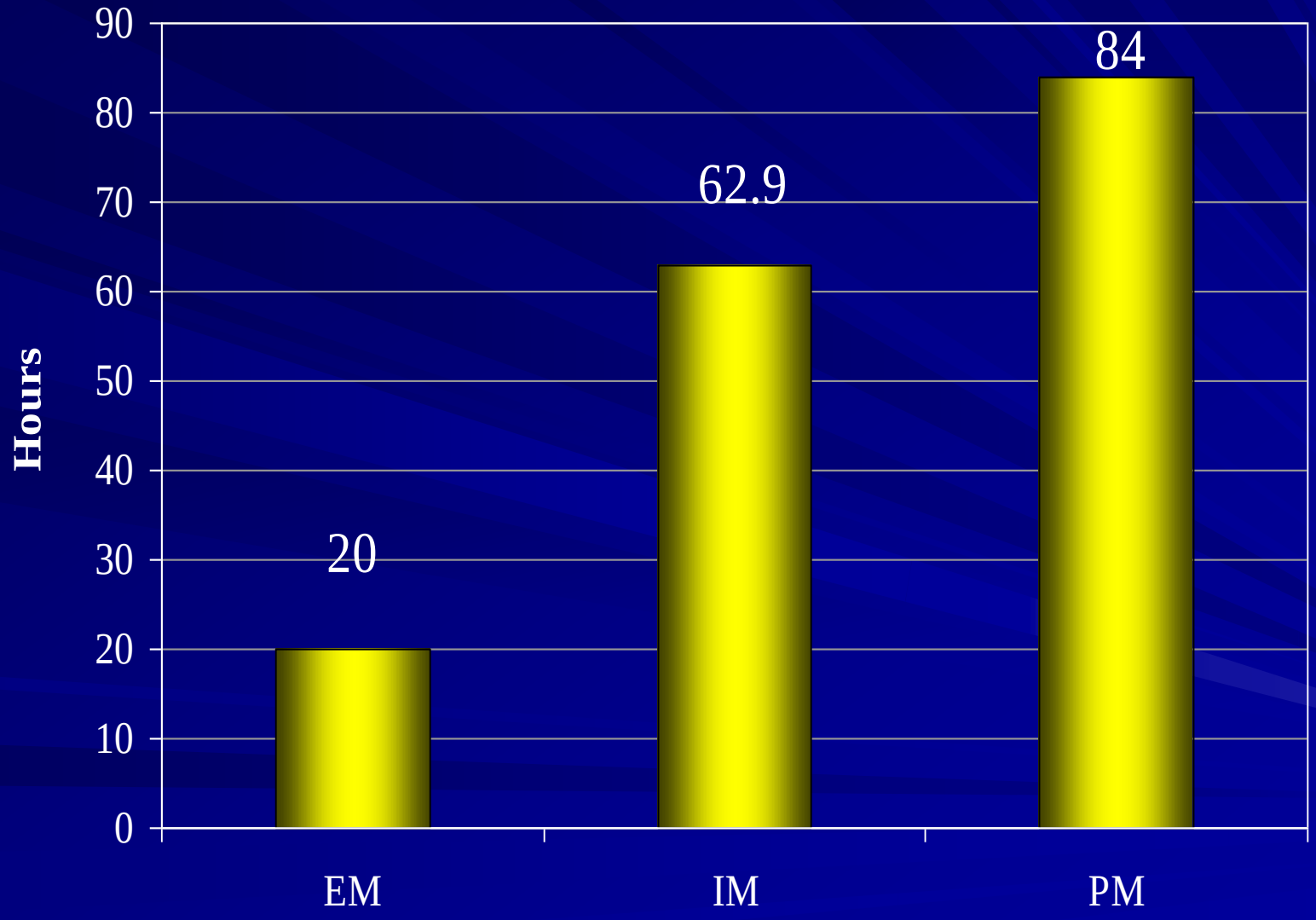
*

Poor Metabolizers (PM) of CYP2C19



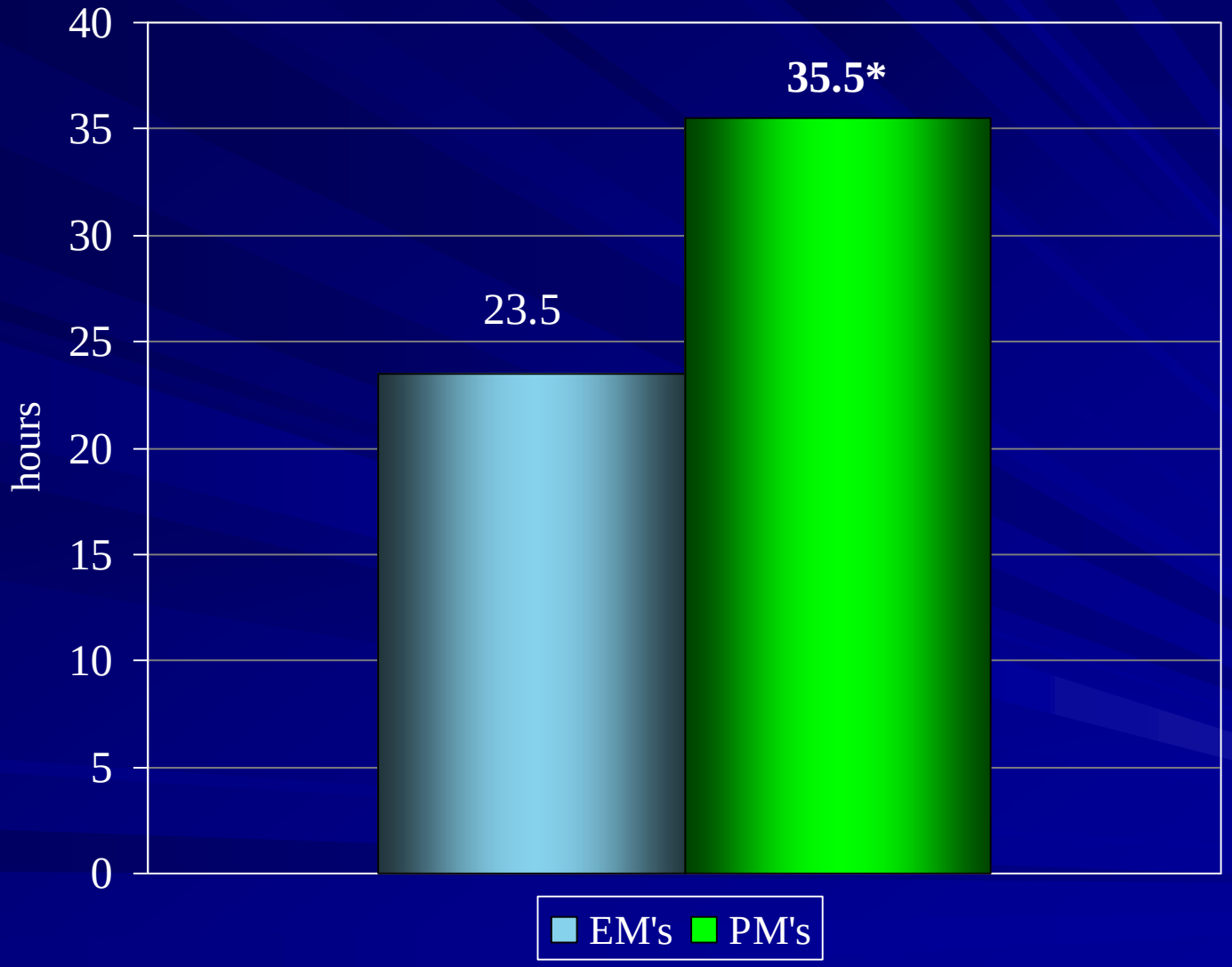
adapted from Smith 2005

CYP2C19 Activity and $t_{1/2}$ of Diazepam in Chinese



Qin et al, 1999

Sertraline $t_{1/2}$ and CYP2C19 Phenotype



*P<.01

Wang et al, 2001

CYP1A2
(Phenacetin *O*-deethylase)

- Inter-ethnic differences (-)
- Polymorphism (+)
- 12%-13% of whites, Africans, and Asians having little or no activity of this enzyme

- Highly inducible by

  charbroiled beef, constituents of tobacco, industrial toxins, and cruciferous vegetables such as cabbage, broccoli, and cauliflower

Richelson 1997

*

CYP1A2 Substrates

Antidepressants:

amitriptyline, imipramine, fluvoxamine

Antipsychotics:

clozapine, fluphenazine, haloperidol, olanzapine, thiothixine

Misc.:

acetaminophen, caffeine, cyclobenzaprine, estradiol, mexiletine, naproxen, ondansetron, propranalol, riluzole, ropivacaine, theophylline, tacrine, zileuton, zolmitriptan

Adapted from Smith 2005

*

CYP1A2 Inhibitors & Inducers

- Inhibitors
  - Amiodarone, cimetidine, ciprofloxin, enoxacin, fluvoxamine, furafylline, grepafloxacin, methoxsalen, mibefradil, norfloxacin, perfloxacin, pipemidic acid, ritanovir, ticlopidine, tosufloxacin
- Inducers
  - Carbamazepine, phenobarbital, phenytoin

de Leon , et al, 2005

*

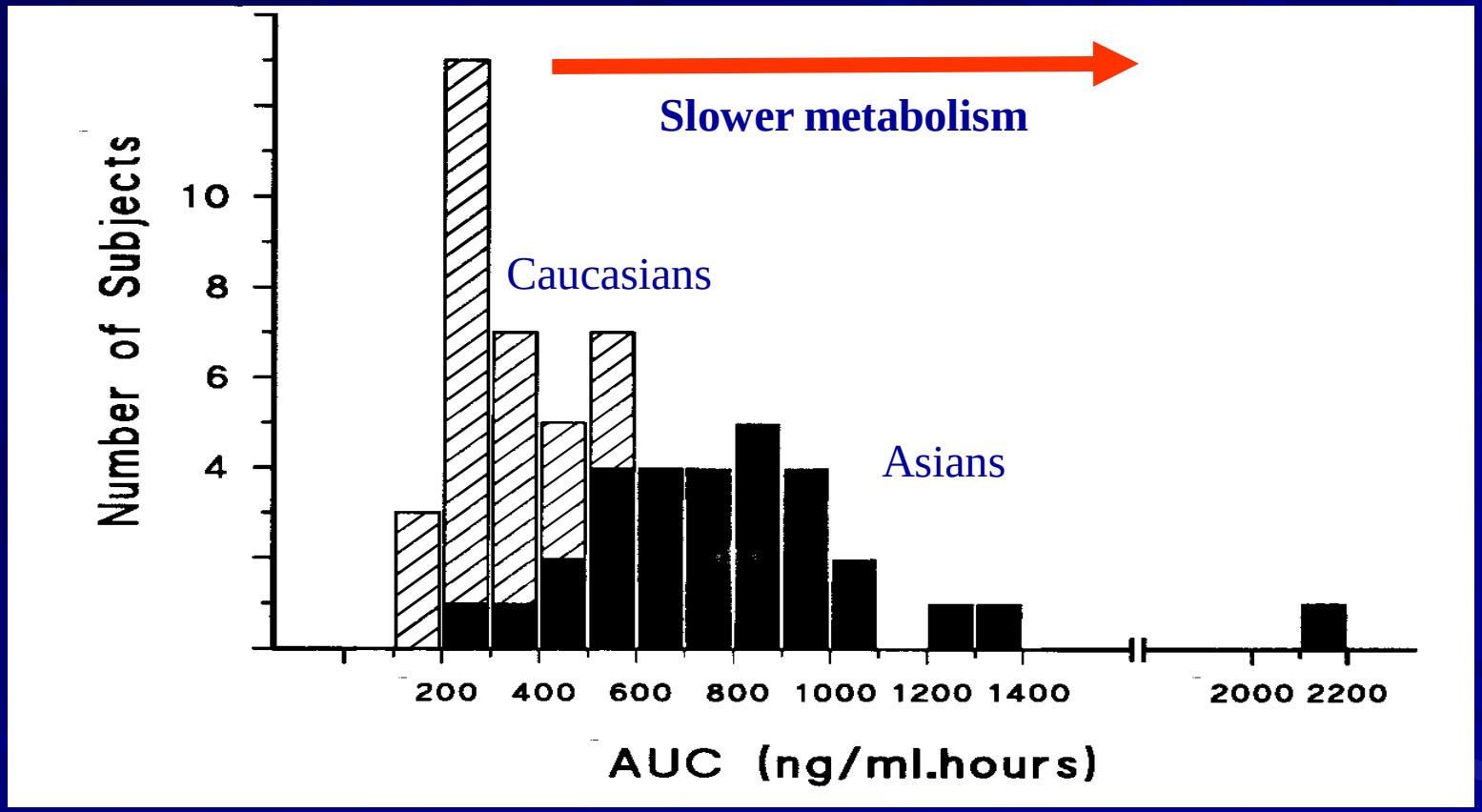
CYP3A4
(Nifedipine oxidase)

- Inter-ethnic differences:
  - Asians have lower enzyme activity than whites, likely due to diet or other environmental factors
  - Polymorphism (-) Readily inducible by carbamazepine and steroids, as well as inhibited by dietary compounds such as naringin, an ingredient of grapefruit juice

Sjoqvist et al, 1997; Richelson 1997

*

Nifedipine Metabolism in Asian Indians and British Caucasians



Asians have lower enzyme activity than whites, likely due to diet or other environmental factors

Sowunmi et al, 1995

CYP3A4 Substrates

Antipsychotics

- clozapine*, haloperidol* , pimozide, quetiapine, risperidone*, sertindole*, thioridazine*, ziprasidone

Antidepressants/ Mood Stabilizers/ Anticonvulsants

- carbamazepine, ethosuximide*, mirtazepine*, nefazadone, remoxapride, sertraline, tiagabine, trazadone*, zonisamide*,

Benzodiazepines/ Sedative Hypnotics

- alprazolam, buspirone, clonazepam, diazepam*, midazolam, triazolam, zaleplon, zolpidem

Calcium Channel Blockers/ Cardiovascular Agents

- amiodarone, amlodipine, atorvastatin, cerivastatin, diltiazem, felodipine, lercanidipine, lidocaine, lovastatin, nifedipine, nisoldipine, nitrendipine, nimodipine, quinidine, quinine, simvastatin, verapamil

Antibiotics/Antifungals/Immune modulators/Chemotherapy

- clarithromycin, cyclosporine, erthyromycin, dapsone, indinavir, ketaconazole, nelfinavir, saquinavir, ritonavir, taxol*, tamoxifen, vincristine
- alfentanil, astemiazole, chlorpheniramine, cisapride, cocaine, codeine*, estrogens, fentanyl, hydrocortisone, methadone, progesterone, salmeterol, terfenadine, testosterone, sildenafil

Adapted from Smith 2005

*

CYP3A4 Inhibitors & Inducers

- Inhibitors
  - fluoxetine, fluvoxamine, nefazadone, norfluoxetine, clozapine, haloperidol
  - diltiazem, verapamil, gestodene
  - erythromycin, itraconazole, ketoconazole, ritanovir
  - grapefruit juice, corn
- Inducers
  - carbamazepine, dexamethasone, felbamate,
  - mesoridazine, oxcarbazepine, phenobarbital, phenytoin,
  - rifampin, topiramate

Zhou et al, 2005

*

Genetic Polymorphisms Involving Drug Metabolizing Enzymes

	CYP2D6 (PM)	CYP2C19 (PM)	ACE (PM)	ADH2*2	ALDH2*2	α1-AGP Sv
US Caucasians	8.7	2.7	52-68	5-20	0	36-44
Chinese	0.7	5.1	22	92	30	18-47
Eskimoes	-	5-21	5-59	0	43-45	43
Navajo	-	-	-	-	2	-
Mestizos (Mexico City)	-	-	-	10	0-4	54
Cuna (Panama)	0	0	29	-	-	-
Caboclos (Brazil)	-	-	-	10	17	-

Notes:

Numbers reflect frequency of genetic distribution (percentage in population studied)

PM: poor metabolizer phenotype

ACE: acetyltransferase

ADH: alcohol dehydrogenase

ALDH: acetaldehyde dehydrogenase

α1-AGP Sv: alpha-1-acid glycoprotein S variant

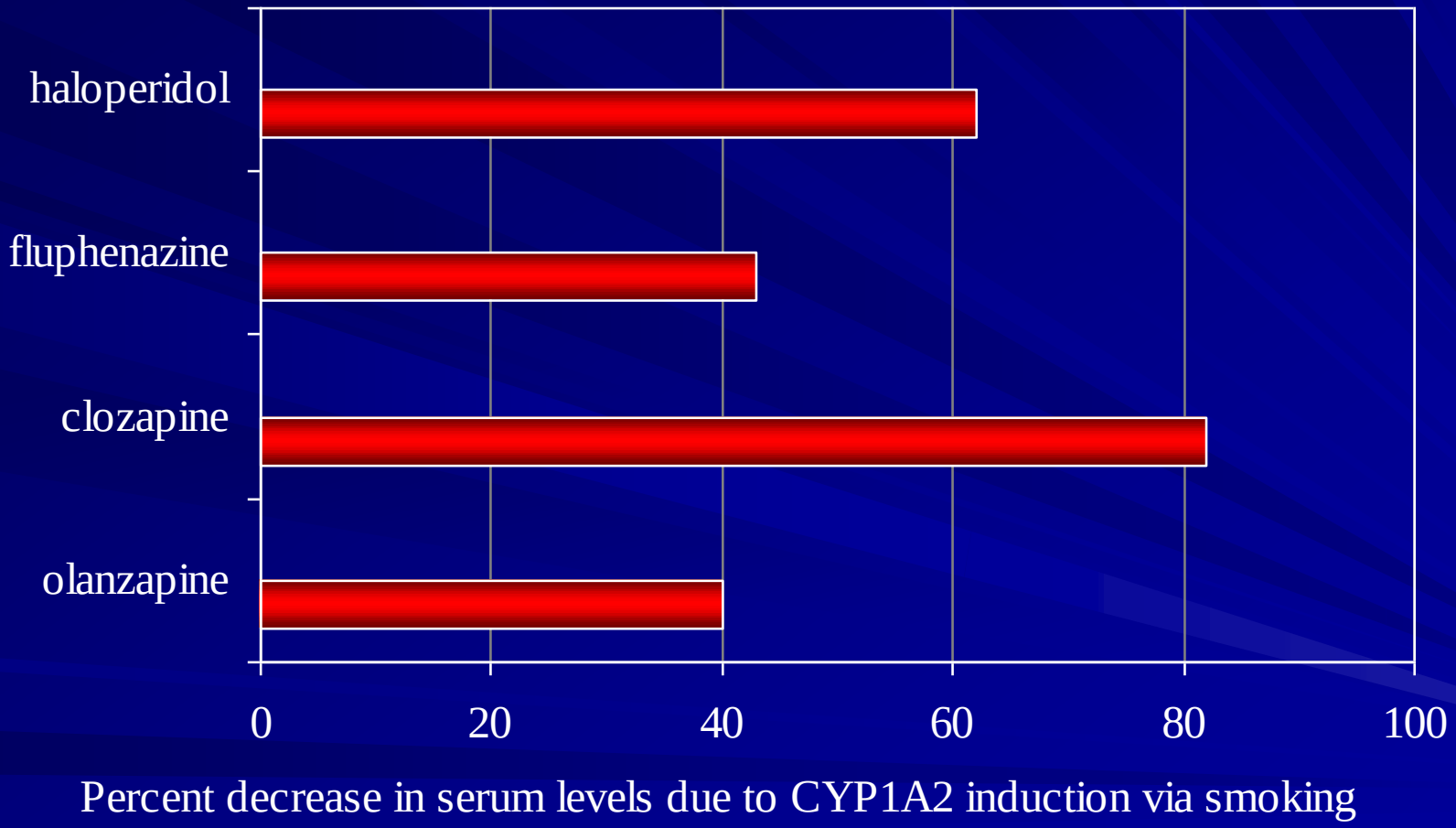
Mendoza et al 1991; Agarwal, et al 1990

Piperine Containing Supplements

- Piperine the active ingredient in black pepper is a potent inhibitor of CYP1A2 & CYP3A4
- The following food supplements contain piperine and may produce interactions with CYP1A2 metabolized medication
  - Acti-Zyyme, Atkins allergy, Atkins blood pressure, Atkins cholesterol, Atkis Cold & Flu, Atkins dieters advantage, Atkins health care, Atkins memory, Atkins menopause, Beyond calcium, Cognicine, DHEA ultra, Diet metabalo-7, Fat binding protein 6, FAT melt - with gymnenema Sylvestre, Hair nutrients, HDT Andropos D 100, Huperzine A Complex, ImmunActin B, Migra Actin, MultiLogics for Men, MultiLogics for Woman, NFA - 500, One Step, PhenSafe, Reliv Arthaffect, Reliv ProVantage, Shen Min, Shen Min - Puritan's Pride, Thermo-Actives, Tribestrone II, Ultra Chondroitin 600

Reen et al, 1996

Smoking and Antipsychotic Response



Bozikas et al, 2004

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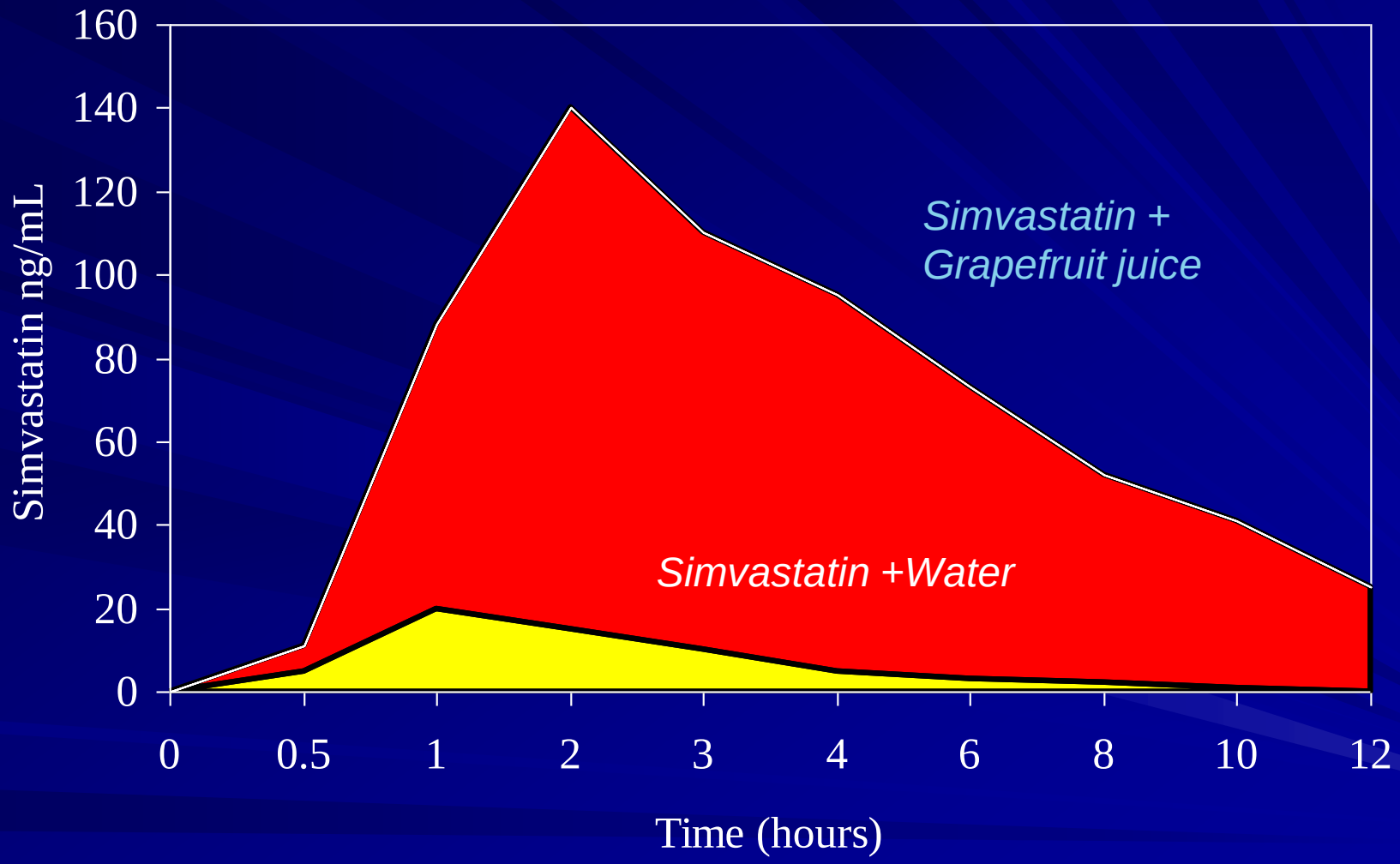
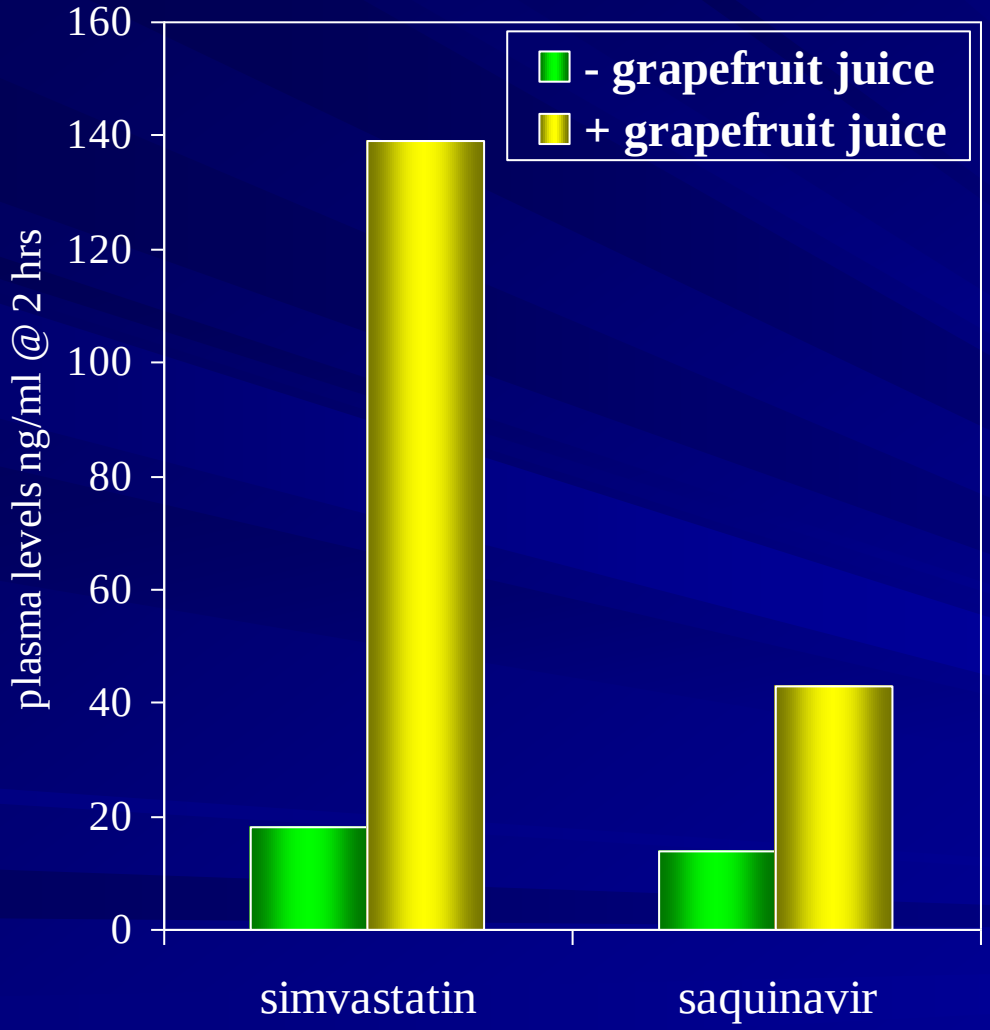
Simvastatin/Grapefruit Juice



Lilja et al, 1998

Grapefruit Juice Inhibits the Metabolism of Simvastatin and Saquinavir



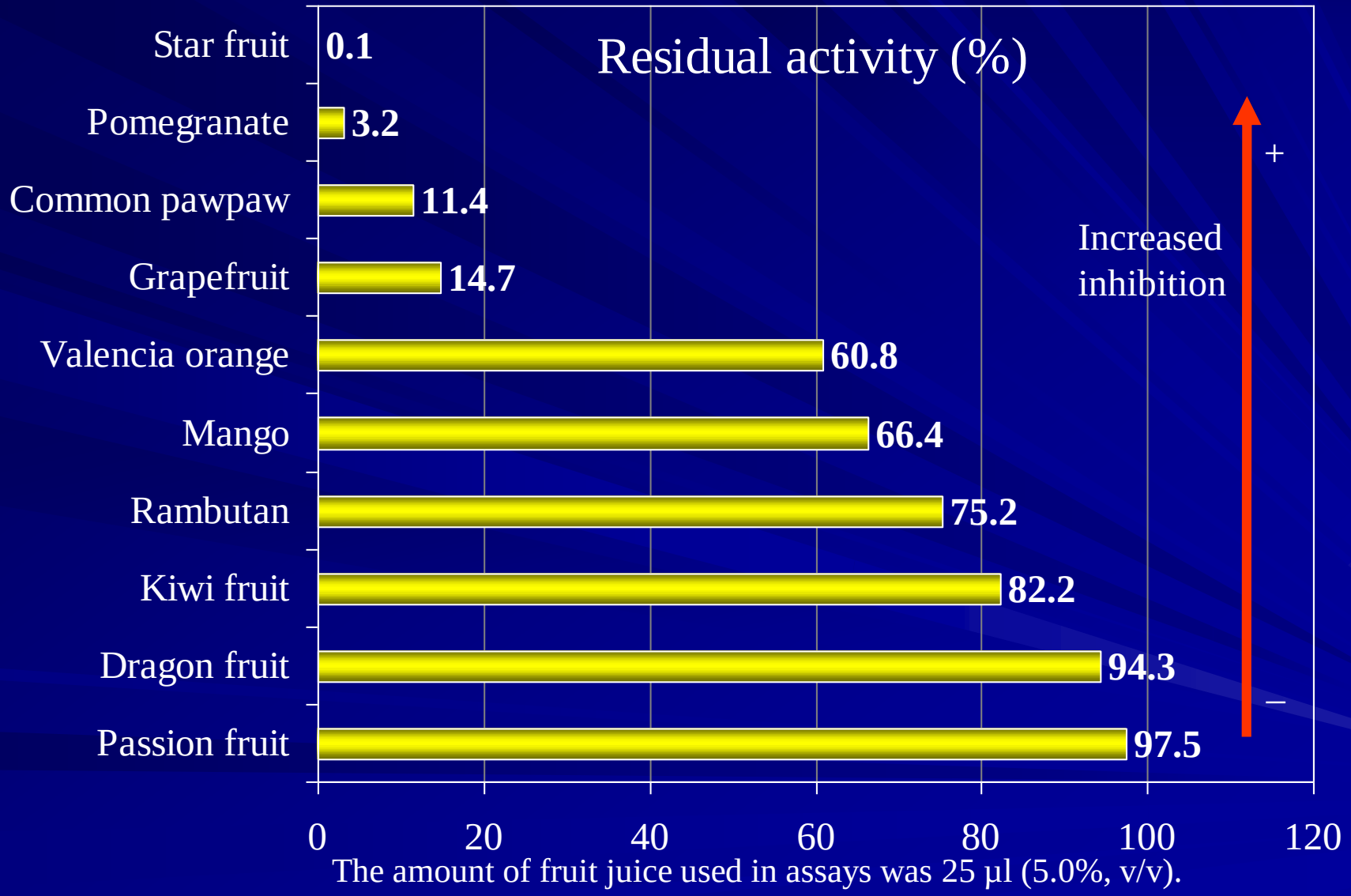
Grapefruit juice is a strong inhibitor of CYP3A4.
It inhibits the enzyme in the small intestine which allows more drug to be absorbed into the bloodstream.

Drugs reported to show Increases when combined with grapefruit juice include: felodipine, nifedipine, verapamil, terfenadine, ethinylestradiol, midazolam, saquinavir, and cyclosporin A

Lilja et al, 1998, Lown et al, 1997

*

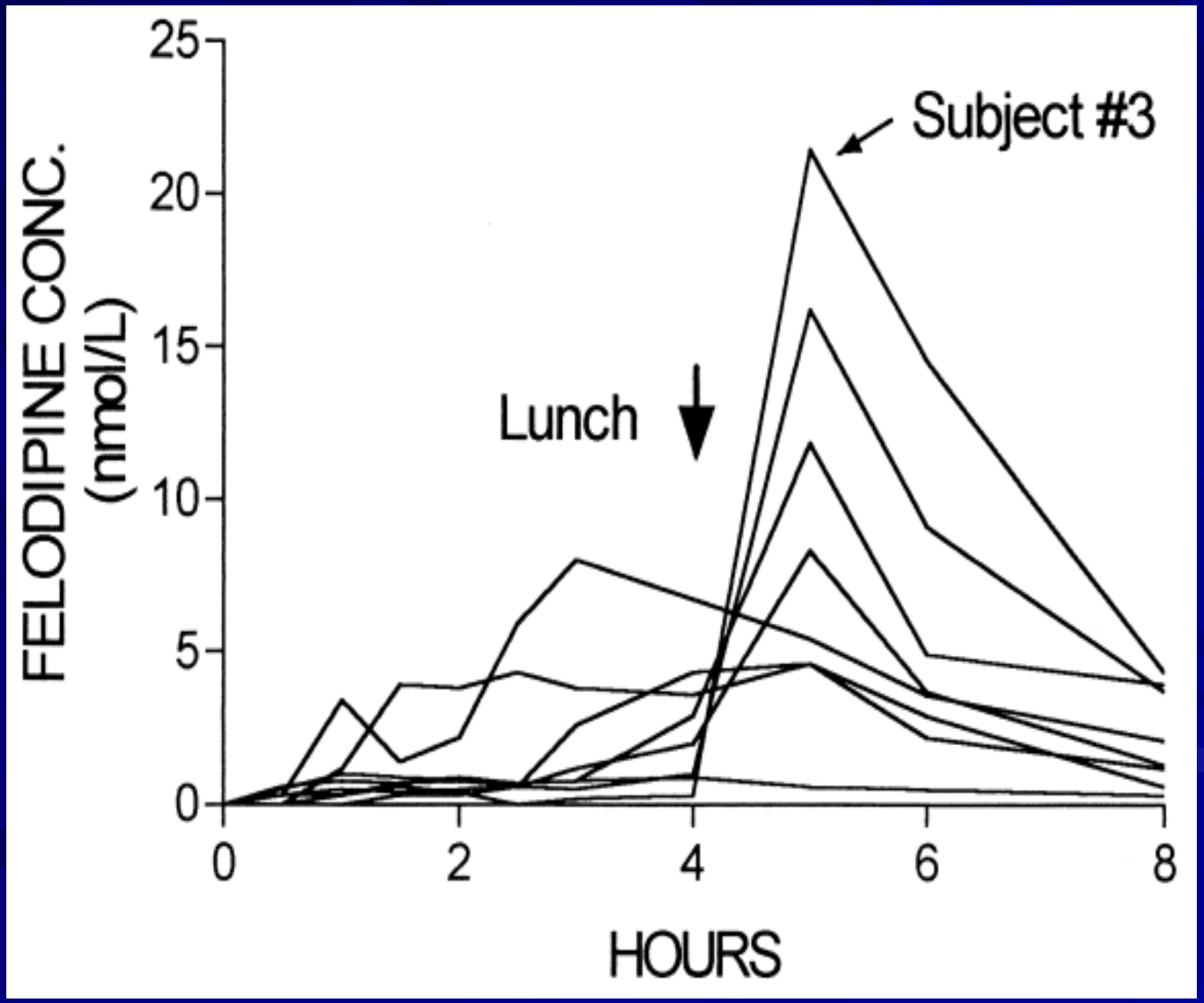
Effects of Tropical Fruit Juice on In-vitro CYP3A4 Activity



The amount of fruit juice used in assays was 25 µl (5.0%, v/v).

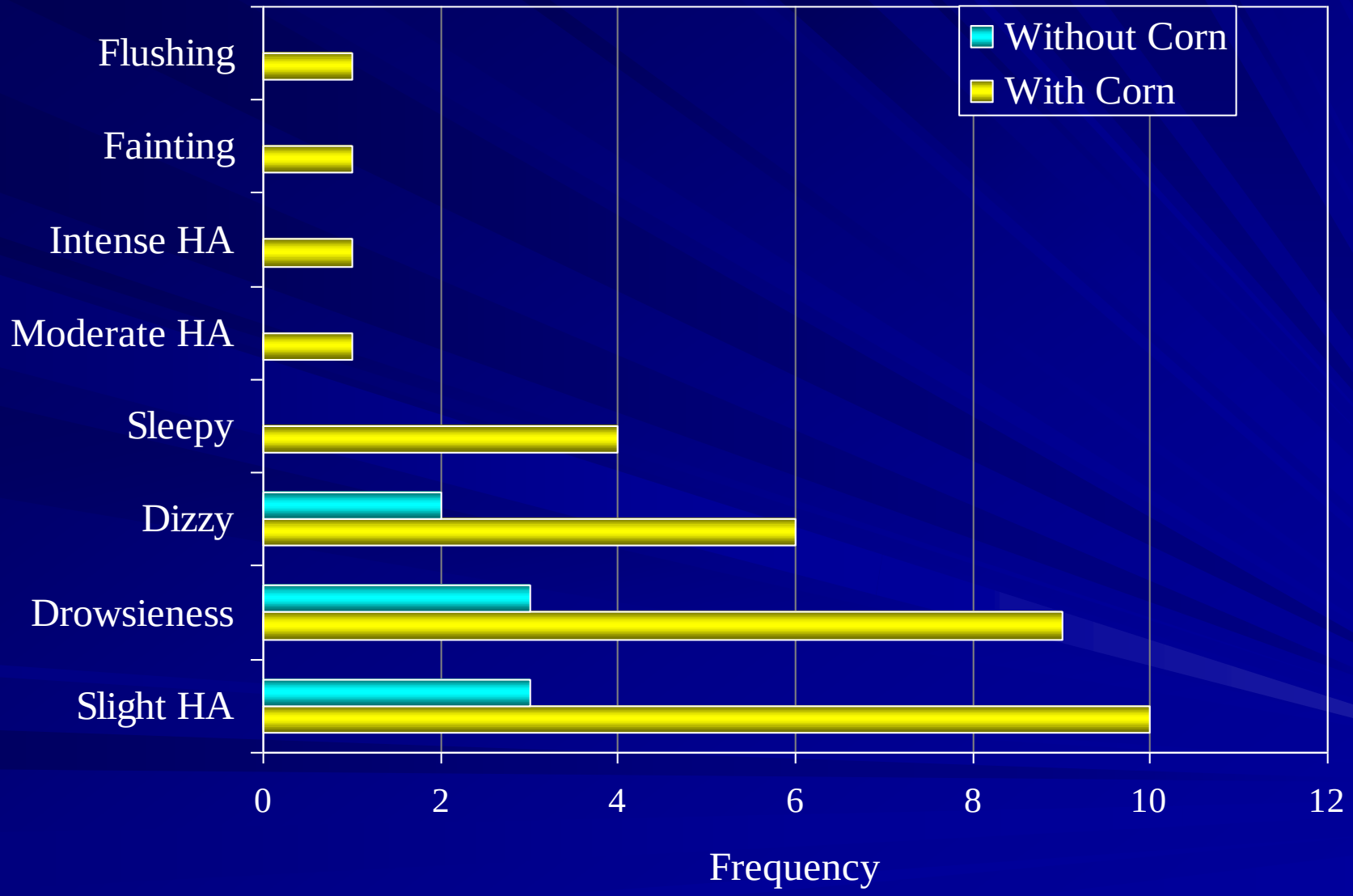
Hidaka et al, Drug Metab Dispos. 2004

Felodipine, & Cabernet Sauvignon



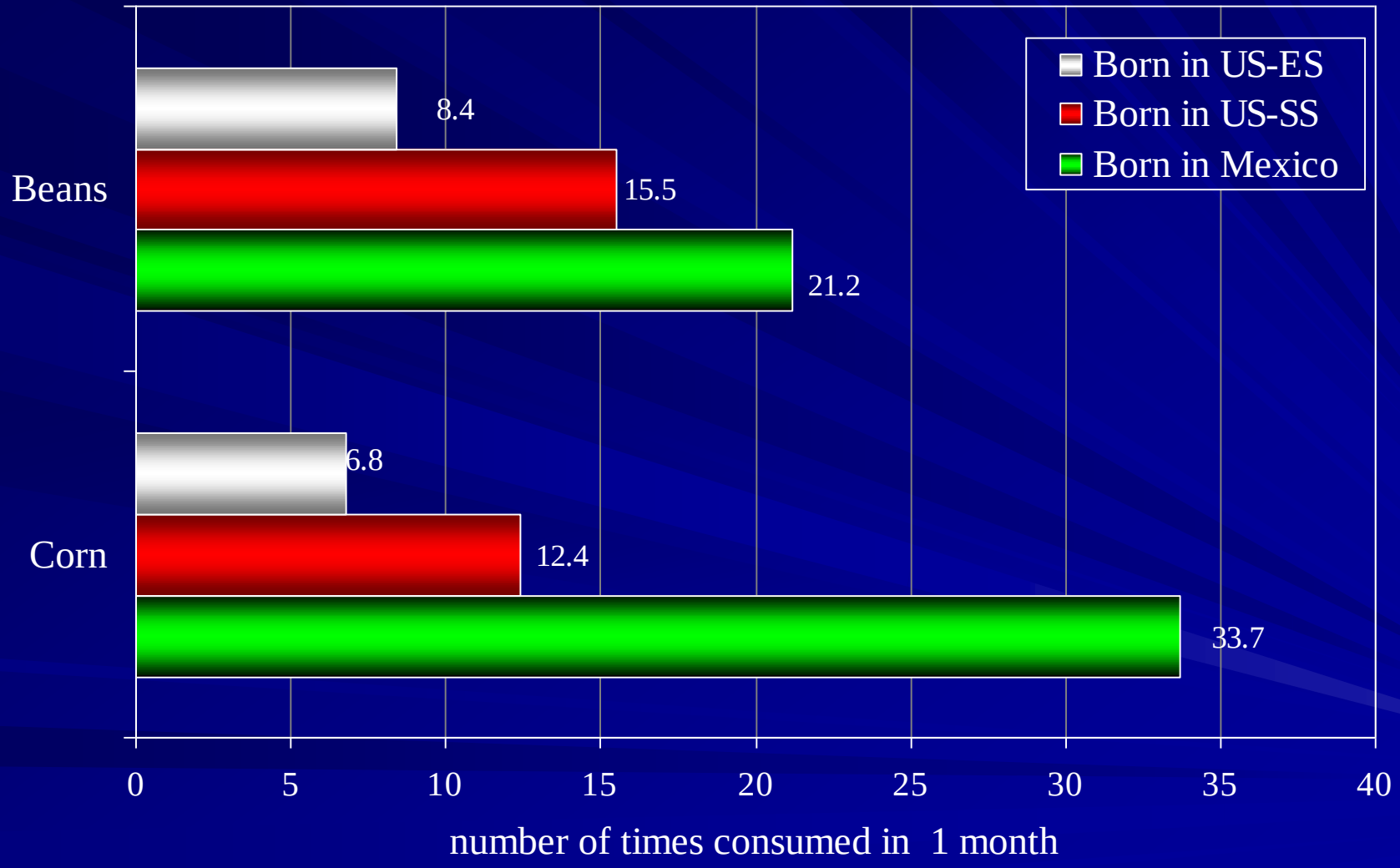
Bailey et al, 2003

Nifedipine Side Effects and Corn



Palma-Aguire, 1999

Diet Variation, Migration & Acculturation Among Mexican American Women



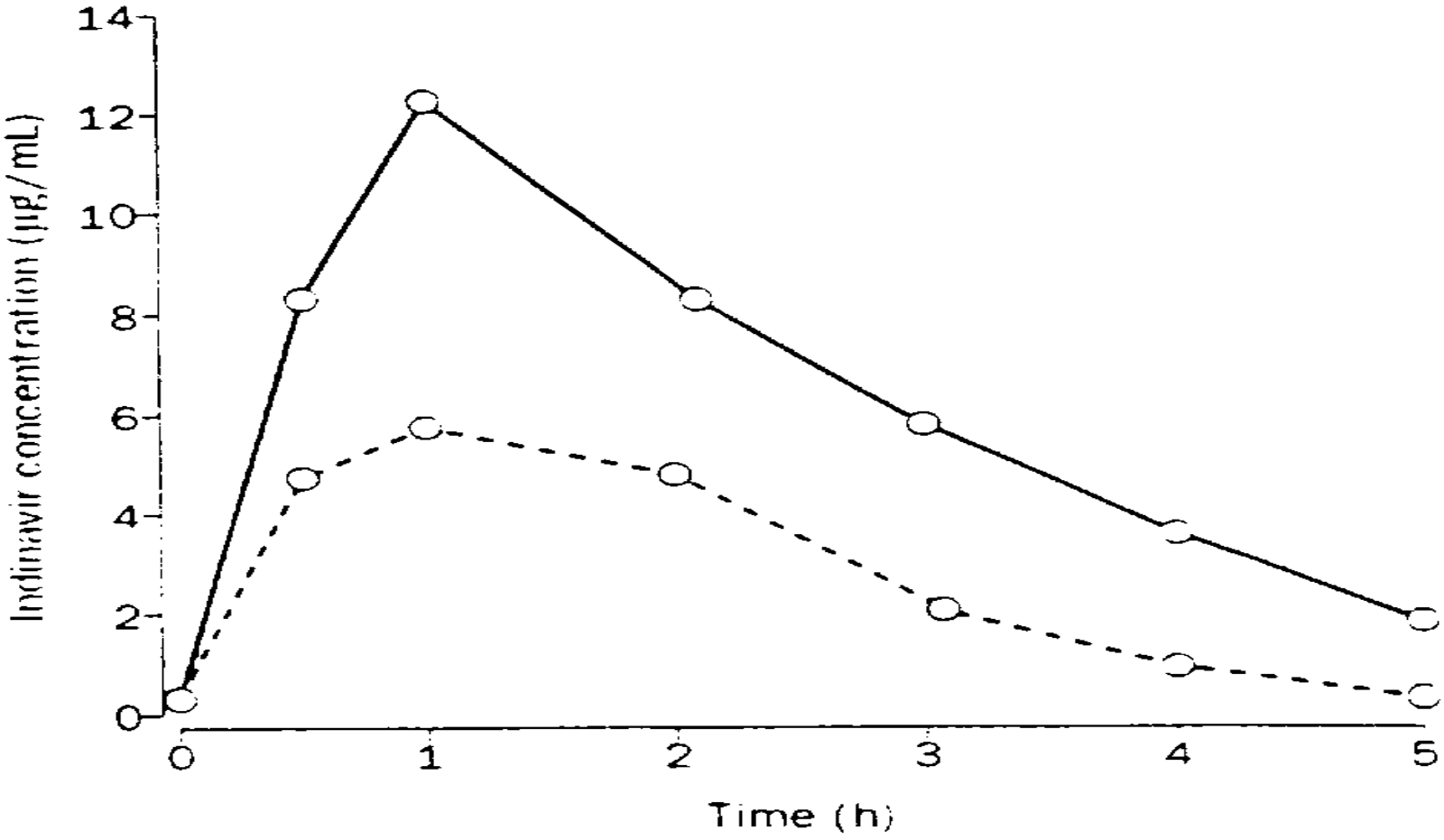
Dixon et al, 2000

Citrus Aurantum Containing Supplements

- Citrus Aurantum which is used in both Chinese and Hispanic herbal medicine has been found ton be a stronger inhibitor of CYP3A4 then Grapefruit juice
- Acutrim Natural A.M., Adrenerlin, Allergia, Allergy Relief, Athletica, Citratherm, Citri-Caps, Citri-Caps Plus, Coldflua, Diet Support Formula, Energiza, Exandra Lean, Fen-Tastic, GlycoLean Manager, GO-lite/fm (Fat Metabolizer), Hepato-C, Herbal Lite, HerbaSlim, Metabosurge, Naturally Herbal Phen, Phen-Free, PhenSafe, Pinnacle Thermophen, Pre, ProLab Stoked, Sharp Thinking, Synadrene, Thermicore, Thermo-Lift (ThermoLift), Thermo-Lift II (ThermoLift II), ThermoSyn, THERMO thin, Trim Fit, Ultra Diet-Phen, UltraAC, UltraAP Activated Pyruvate, Vigrex, Xenadrine RFA-1, Xtra Fuel, Xtreme Trim

Malhotra et al, 2001

Indinavir & St. John's wort



Mean concentration-time of indinavir alone (solid line) and with concomitant St John's wort (dotted line)

Piscitelli et al, 2000

Herb- CYP450 Drug Interactions

Drug-A	Herbal-B	P450	Interaction
Ciprofloxin Enoxacin Pipemidic acid Fluvoxamine	Coffee arabica Llex paullina Yerba mate	1A2 inhibition	 Increased conc. B Caffeine toxicity
Theophyline Phenytoin	Piper longum Piper nigum	1A2 inhibition	Increased conc. A
	Licorice	1A2 induction	Decreased conc. A
Quinidine Haloperidol Moclobemide	sparteine in Cytisus scoparius	2D6 inhibition	 Increased conc. B Circulatory collapse
Nifedipine Seldane, xanax	grapefruit, corn Panax ginseng Ginkgo biloba	3A4 inhibition	 Increased conc. A Increased effects
Cyclosporine Digoxin, Indinavir Amitriptyline	St. John's wort Licorice	? Induction	 Decreased conc. A Decreased effects

Adapted from Smith 2005

The Ethnopsychopharmacological Approach:

- **Assessment**
  - Cultural formulation for Diagnosis
- **Choice of Medication**
  - Use medical history, concurrent medications, diet and food supplements / herbals combined with knowledge of enzyme activity in certain ethnic groups
- **Monitor Patient**
  - Proceed slowly- Involve family
  - If side effects intolerable - lower dosage, or choose drug metabolized through different route
  - If no response-check compliance, raise dose and monitor levels, add inhibitors, switch drug

Major Teaching Points

- Society has become more ethnically and culturally diverse
- An understanding of cross-cultural perspectives in psychopharmacology has become essential for psychiatrists
- Prescribe therapeutic regimen to be culturally appropriate
- Adhere to the basic principle of rational psychopharmacotherapy, that is, to prescribe the lowest possible dose for the shortest duration, maximizing therapeutic effects while minimizing side effects for every patient from different ethnic and cultural backgrounds
- Apply integrative approach in which biological, ethnic, and cultural diversity are taking into account and treatment is tailored to specific individual characteristics

Pi & Simpson, 2005

Post-lecture Examination Questions 1

Which of the following statements are correct?

1. Pharmacogenetic profile can influence both the pharmacokinetics and the pharmacodynamics of a given medication.

2. Pharmacokinetics refers the way in which the body handles drugs. This includes absorption, distribution, metabolism (biotransformation) and excretion (elimination).

3. Pharmacodynamics refers to the effects of a drug on the body such as tissue or receptor sensitivity. This explains some ethnic differences in therapeutic doses/effects and side effects of various psychotropic medications.

A. 1 and 2
B. 1 and 3
C. 2 and 3
D. All of the above

Post-lecture Examination Questions 2

Which of the following statements are correct?

1. African Americans presenting with affective disorders are apt to be misdiagnosed or over-diagnosed as having schizophrenia.

2. African Americans tend to receive higher dosages of antipsychotic medications and more long-acting depot forms than whites.

3. African Americans tend to Less likely to receive second-generation antipsychotics or selective serotonin reuptake inhibitors.

A. 1 and 2
B. 1 and 3
C. 2 and 3
D. All of the above

Post-lecture Examination Questions 3

Which of the following statements are correct?

1. Hispanic Americans are more apt to focus on somatic complaints in depressed.

2. Hispanic Americans require lower doses (1/2) of antidepressants than whites.

3. Hispanic Americans experience more anticholinergic side effects than whites.

A. 1 and 2
B. 1 and 3
C. 2 and 3
D. All of the above

Post-lecture Examination Questions 4

Which of the following statements are correct?

1. Asian Americans tend to present with somatic rather than psychological complaints and seek help from primary care physicians.

2. Asian Americans experience a greater incidence of extrapyramidal side effects (EPS) then whites and African Americans Hispanic Americans require lower doses (1/2) of antidepressants than whites.

3. Asian patients receive lower doses and have higher plasma levels of antipsychotics than whites.

A. 1 and 2
B. 1 and 3
C. 2 and 3
D. All of the above

Post-lecture Examination Questions 5

Which of the following ethnic groups has the highest percentage of poor metabolizers (PM) of P450 2D6, the enzyme involved in the metabolism of a large number of psychotropic medications?

A. Whites
B. Hispanic Americans
C. African Americans
D. Asian Americans

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