CROSS-CULTURAL PSYCHOPHARMACOLOGY

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Please note that crucial slides are marked with an asterisk in the bottom right corner

Pre-lecture Examination Question 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

Pre-lecture Examination Question 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

Pre-lecture Examination Question 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

Pre-lecture Examination Question 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

Pre-lecture Examination Question 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

Cross-cultural Psychopharmacology

- A branch of science seeks to determine whether differences exist between ethnic groups in their response to psychotropic edications, as well as the reasons for such variations, including genetic, biological, environmental, and psychosocial factors

- Determines whether differences exist in the pharmacokinetics and pharmacodynamics among various ethnic groups and ,where present, to determine the reasons for such variation

Pi and Simpson, 2005

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Asian Culture and Attitudes Toward Mental Illness

- Linguistically and culturally heterogeneous
- Viewed as an embarrassment or stigma by Asian patients and their families
- Tend to delay psychiatric care until they are seriously disturbed when they enter the mental health system, often require psychopharmacotherapy due severe and chronic condition
- “Model minority”

Lin et al, 1982; Kleinman, 1980

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Asian Culture and Attitudes Toward Mental Illness

- Cultural influences on symptoms manifested by Asian patients may mislead clinicians who are unfamiliar with Asian culture and health beliefs
- Expresses problems in behavioral or somatic terms rather than in emotional ones
- Present with somatic rather than psychological complaints and seek help from primary care physicians

Lin et al, 1995

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Asian Culture and Attitudes Toward Mental Illness

- Using indigenous or alternative remedies, and folk or traditional medicine may be tried first
- Assess Herbal medicine interactions, efficacy, toxicity, compliance, and placebo effects, and interpretations and perceptions of side effect

Smith et al, 1993

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Hispanic Americans

- Diverse group (Hispanic/Latino)
- Underutilize mental health services, Folk healers: curanderos, espiritistas, or santeros
- Seek help from non-psychiatrist physicians
- Lower daily doses (30%) of antipsychotic medications
  - Lower doses of clozapine and risperidone
- Similar relationship between plasma haloperidol levels and oral dose in Latinos and in non-Latino whites

Collazo et al, & Ruiz et al, 1996; Ramirez, 1996; Jann et al, 1993; Carno et al, 1969; Trevino & Rendon, 1994

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African Americans

- Misdiagnosis / Over-diagnosis of schizophrenia
- Receive higher dosages of antipsychotic medications
- More sensitive to the effects of antipsychotic medications
- More long-acting depot forms prescribed
- Less likely to receive second-generation antipsychotics or selective serotonin reuptake inhibitors

Walkup et al, 2000; Bell, 1996; Segal et al, 1996; Lawson, 1986 Kuno and Rothbard, 2002; Price et al, 1985; Herbeck et al, 2004; Kuno and Rothbard, 2002; Melfi et al, 2000

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African Americans

- Tardive Dyskinesia
  - No differences in the prevalence
  - 1.8 times more likely than Caucasians
- Twice the annual incidence of TD as Caucasians
- Factors: Unclear

Sramek et al, 1991; Glazer et al,1994; Jeste et al, 1995

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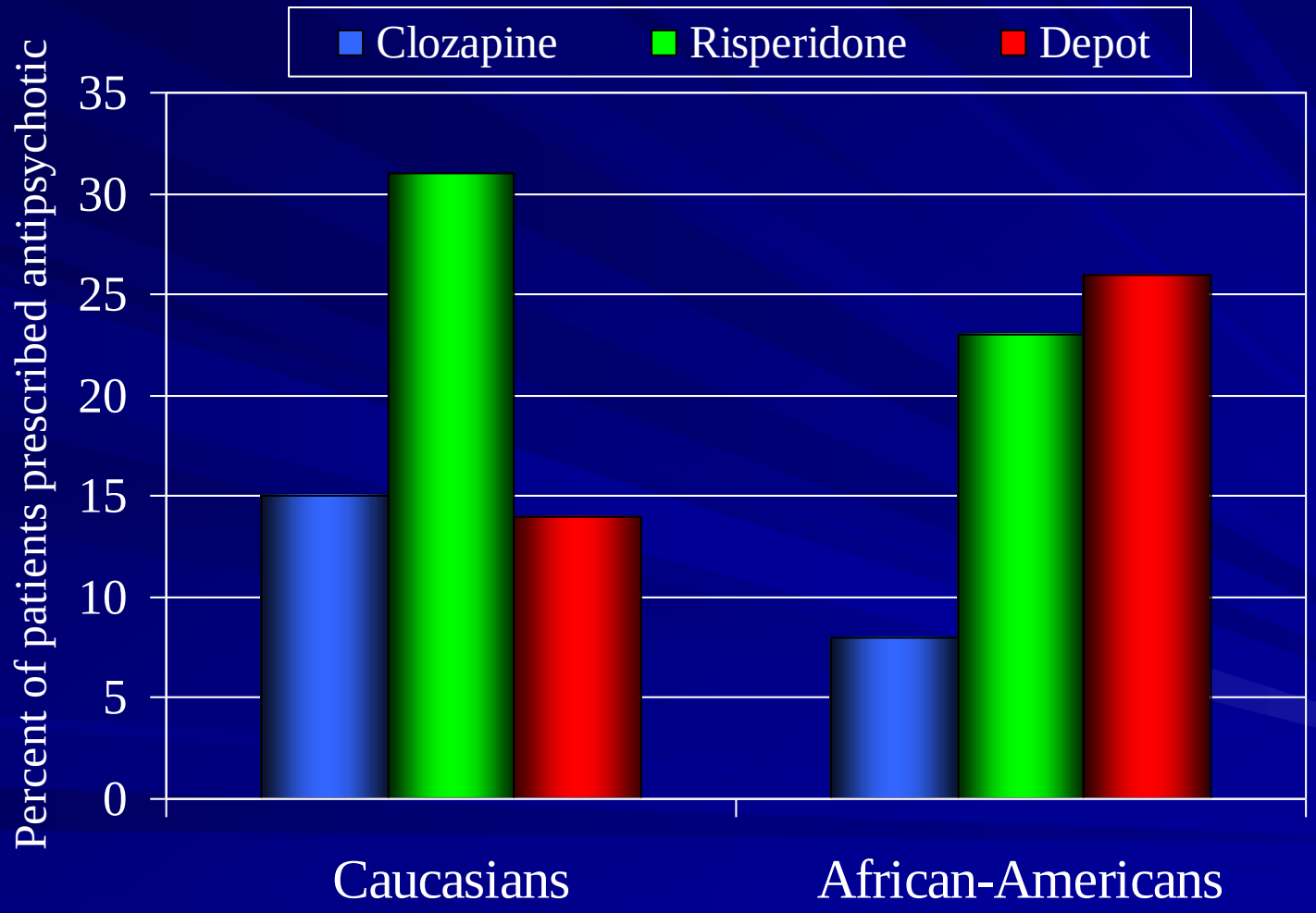
Racial Disparities in Antipsychotic Prescription Patterns



Kuno & Rothbard, 2002

Antipsychotics: Lu 1987

- Retrospective chart review of 158 admissions at San Francisco General Hospital of African American, Asian, Caucasian, and Hispanic patients
  - maximal neuroleptic dose.
  - discharge dose
  - EPS
  - dose associated with EPS
- No Ethnic differences noted
- Immigrant Asians and Hispanics-lower mean maximal neuroleptic dose compared to U.S. born

Asian Americans
Antipsychotics (Neuroleptics)

- Asian patients received lower doses than Caucasians
- No differences in the average daily doses

Lin and Finder, 1983; Ruiz et al, 1996; Sramek et al, 1986

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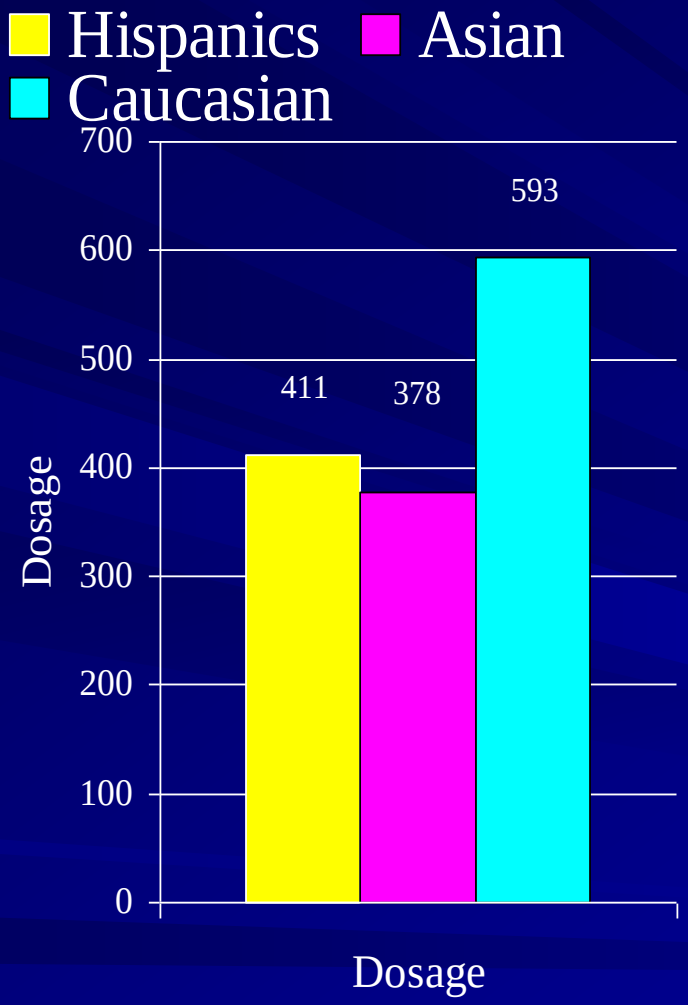
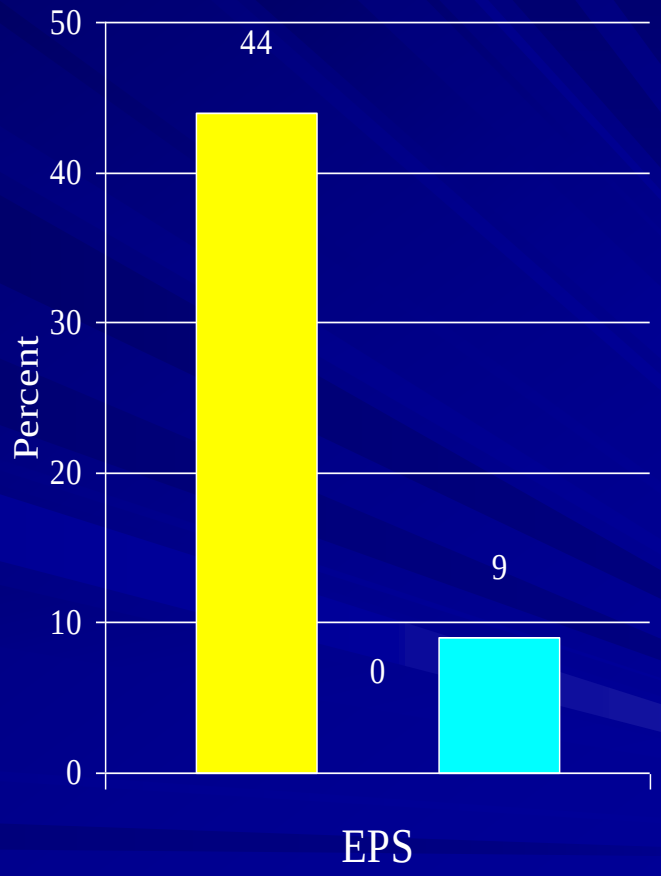
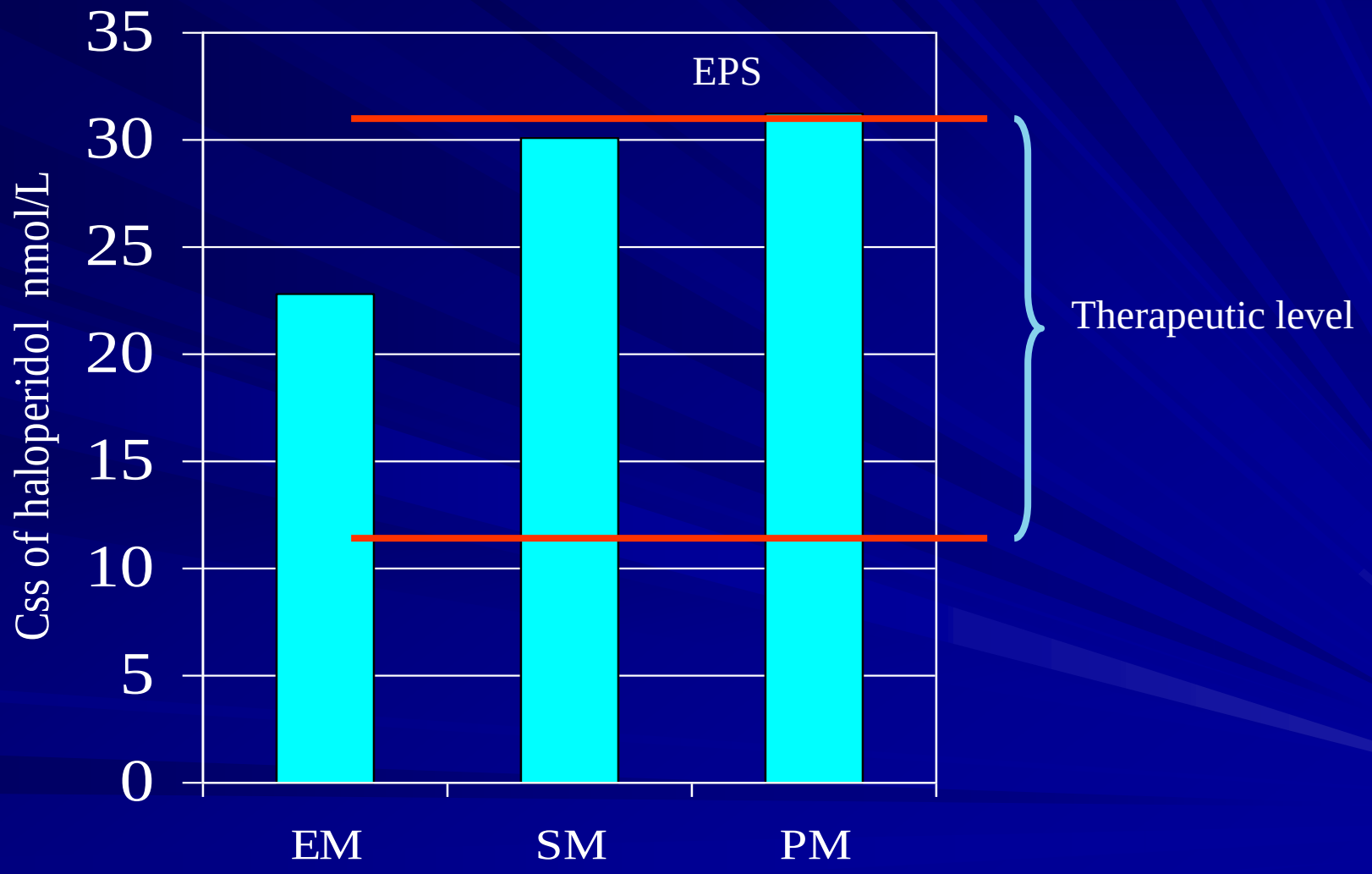
Antipsychotics: Collazo et al 1996



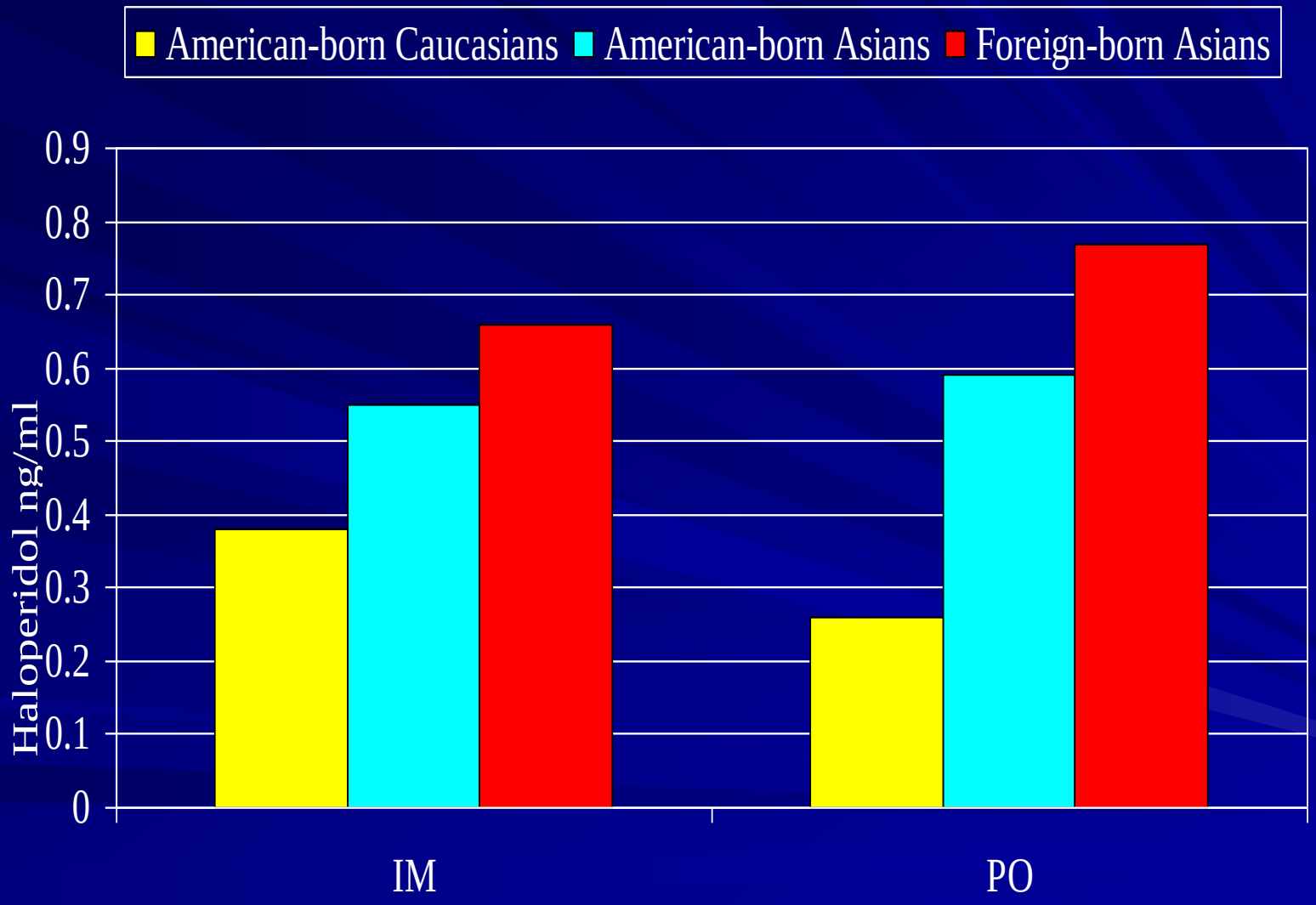


Asian Americans: Antipsychotics Haloperidol and the CYP2D6*10 allele



Milhard et al, 1999

Asian Americans: Antipsychotics
Haloperidol: Lin et al. 1988



Asian Americans
Antipsychotics (Neuroleptics)

Pharmacokinetic studies:

- Higher plasma levels of antipsychotics than Caucasians:
- Plasma haloperidol levels to be 52% higher in the Chinese than in the Americans
- Caucasians had lower serum haloperidol and prolactin levels than Asians (both American and foreign-born)

Potkin et al, 1984; Lin et al, 1988

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Asian Americans
Antipsychotic Medication-Induced Movement Disorders

- Acute dystonic reactions:
  - Asian patients experienced higher rate than white patients
- Akathisia:
  - Less is known
  - Asian patients experienced lower rate than white patients

Ko et al, 1989; Binder and Levy 1981; Binder and Levy 1981

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Asian Americans
Antipsychotic Medication-Induced Movement Disorders

- Parkinsonism:
  - Asian patients developed symptoms while taking lower doses and exhibiting lower serum haloperidol levels than Caucasian patients
  - Little difference between Asian patients (40%) and Caucasian patients (35%)
  - 18%-40% in Japanese patients, comparable to rates in the US

Lin et al, 1989; Binder and Levy 1981; Binder et al, 1987

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Asian Americans
Antipsychotic Medication-Induced Movement Disorders

- Tardive dyskinesia (TD):
  - Overall prevalence

    11% from Asian studies,

    versus

    28% from North American studies

Gray and Pi 1998

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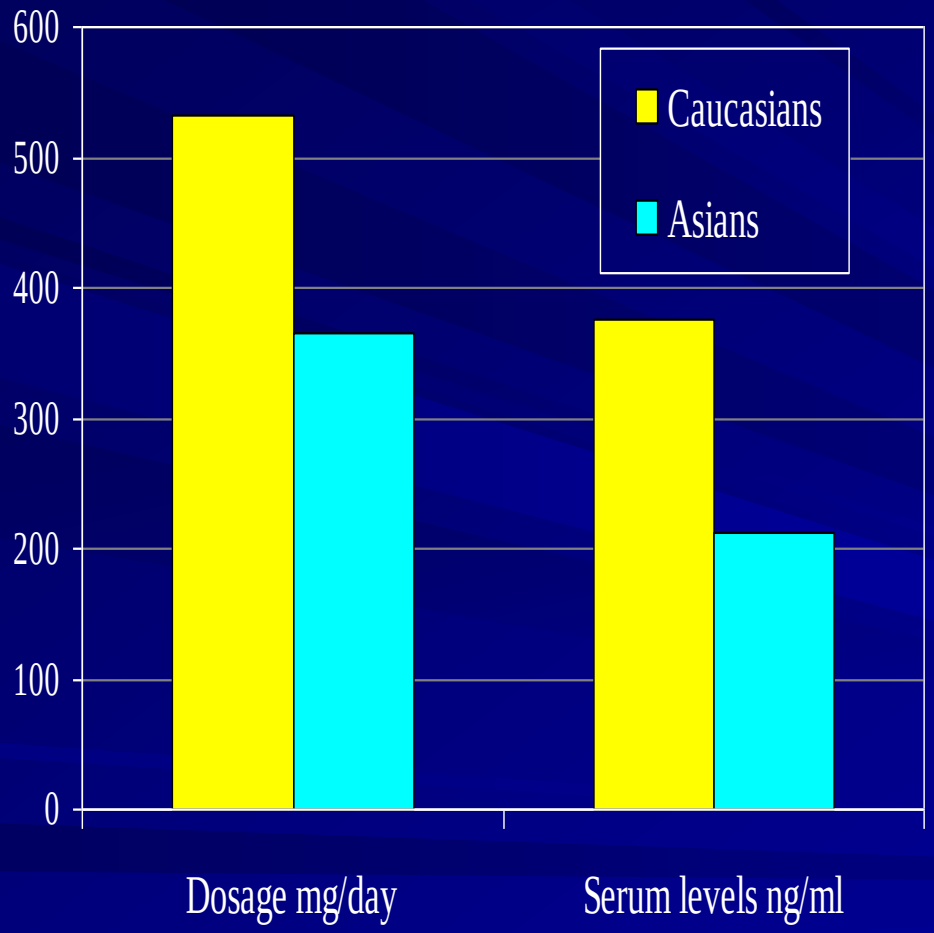
Asian Americans: Antipsychotics
Clozapine: Dosage, Serum Levels, & Response



Koreans attending outpatient psychiatric clinics in Los Angeles were noted to receive lower doses of clozapine, have lower blood levels, higher rates of anticholinergic side effects, and better response than Caucasian patients in the study.

Matsuda et al, 1996

Ethnicity & Clozapine

- African Americans
  - Benign Neutropenia prevents selection for clozapine
  - Low white count may result in discontinuation
- Asians
  - Often excluded due to selection criteria
  - Lower dose, higher plasma levels (30-50%)- Chinese
  - Lower dose, increased side effects- Koreans
  - Lower dose - Southeast Asians
  - Higher risk of Agranulocytosis 2.4X
- Hispanics
  - Argentina and Chile - lower doses
- Ashkenazi Jews
  - Increased risk of Agranulocytosis

Adapted from Smith 2005

African Americans
Lithium

- Lithium
  - Higher RBC/serum lithium ratio
  - Differences in Lithium-sodium countertransport
  - No pharmacokinetic differences except a slightly longer elimination half-life

Strickland et al, 1995

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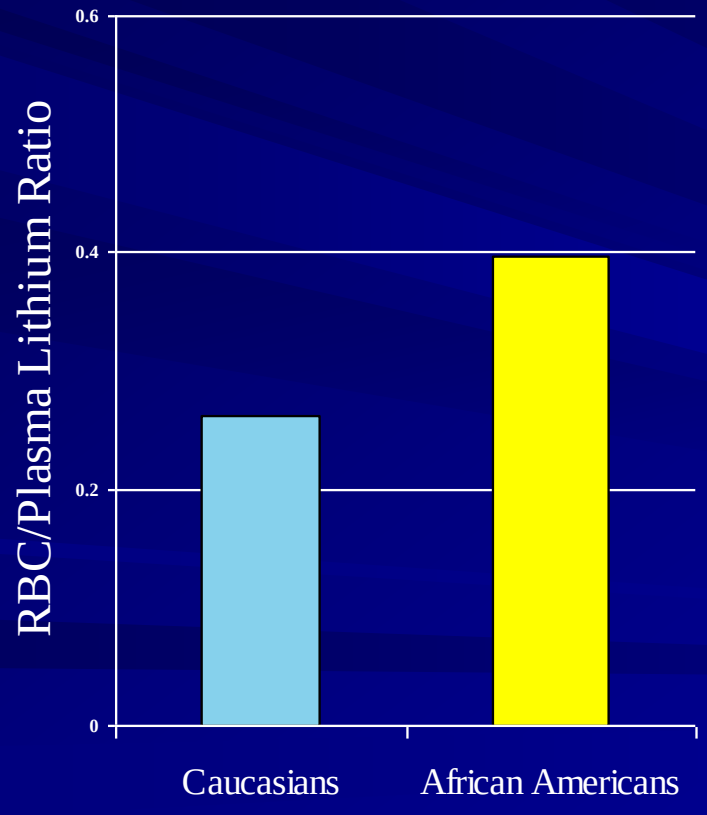
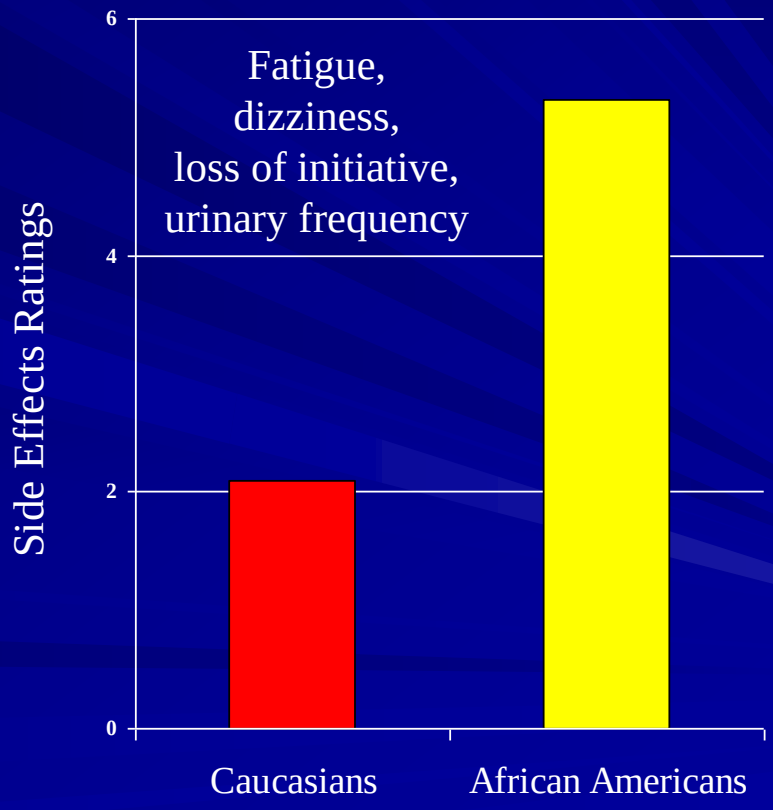
RBC Lithium counter transport associated with side effects in African Americans

RBC/Plasma Lithium Ratio: Ethnic Variation

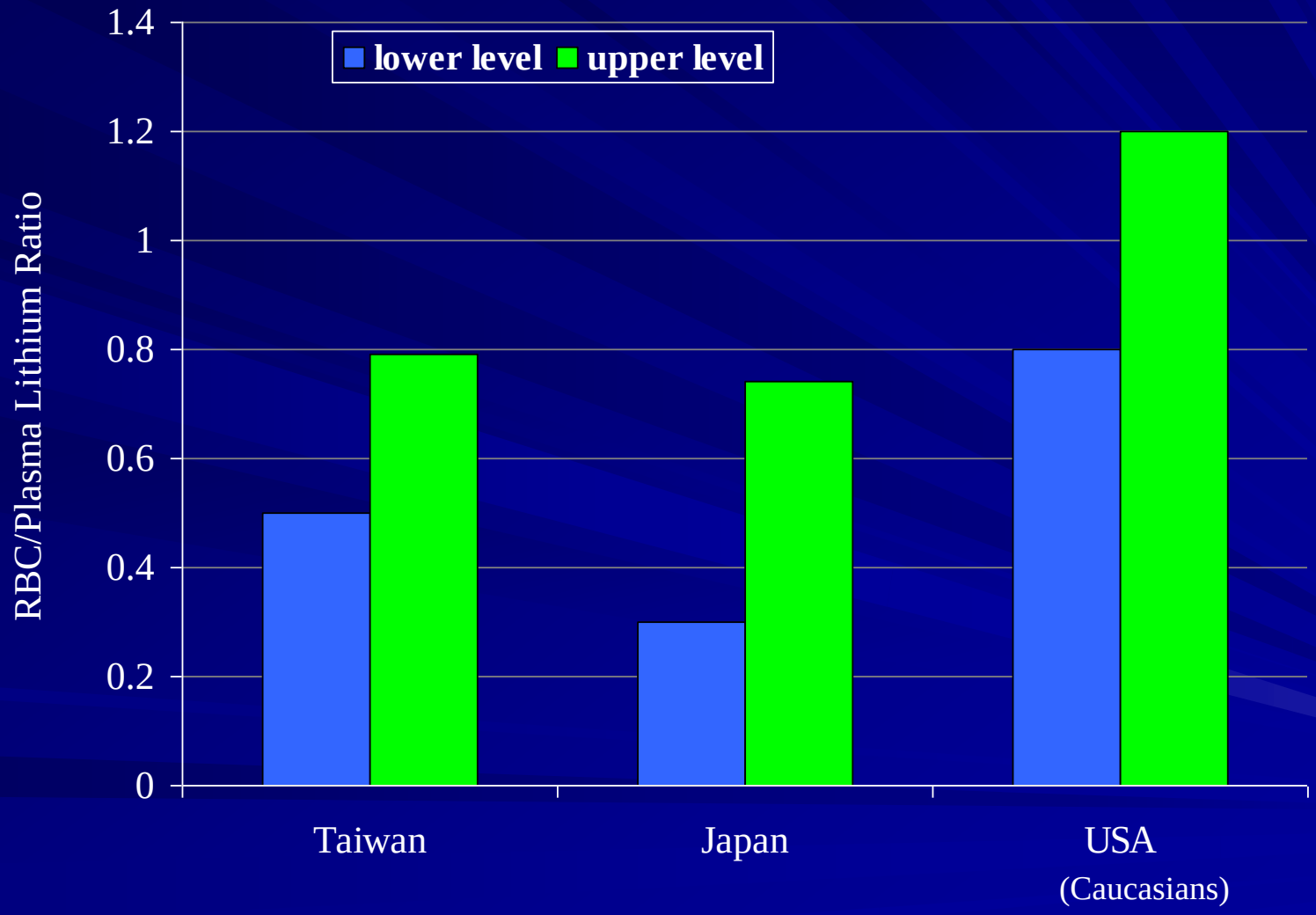


Lithium Side Effects Ratings: Ethnic Variation



Strickland et al. Biol. Psychiatry, 1995

Asians: Therapeutic Lithium Levels:



Yang 1985

Asian Americans
Lithium

- Surveys and case series suggest that Asians may respond to lower doses and plasma levels (0.3-0.9mEq/L) of lithium than non-Asians

- No significant differences in pharmacokinetics of lithium between ethnic groups

Yamamoto et al, 1979; Takahashi 1979; Yang 1985

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Hispanic Americans
Lithium

- Lithium
  - Bipolar patients may be misdiagnosed as schizophrenia
  - Pharmacokinetics and RBC/plasma lithium ratio: ?

Mukherjee et al, 1983

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African Americans
Antidepressants

- Pharmacokinetics of TCAs
  - Higher plasma Levels
- Pharmacodynamics of TCAs
  - More rapid response
  - Increased risk of developing delirium
  - Effective treatment, increased risk of side effects, partly explained by pharmacokinetics

Rudorfer & Robin, 1982; Ziegler & Boggs 1977; Raskin et al, 1975; Livingston et al, 1983; Strickland et al, 1997

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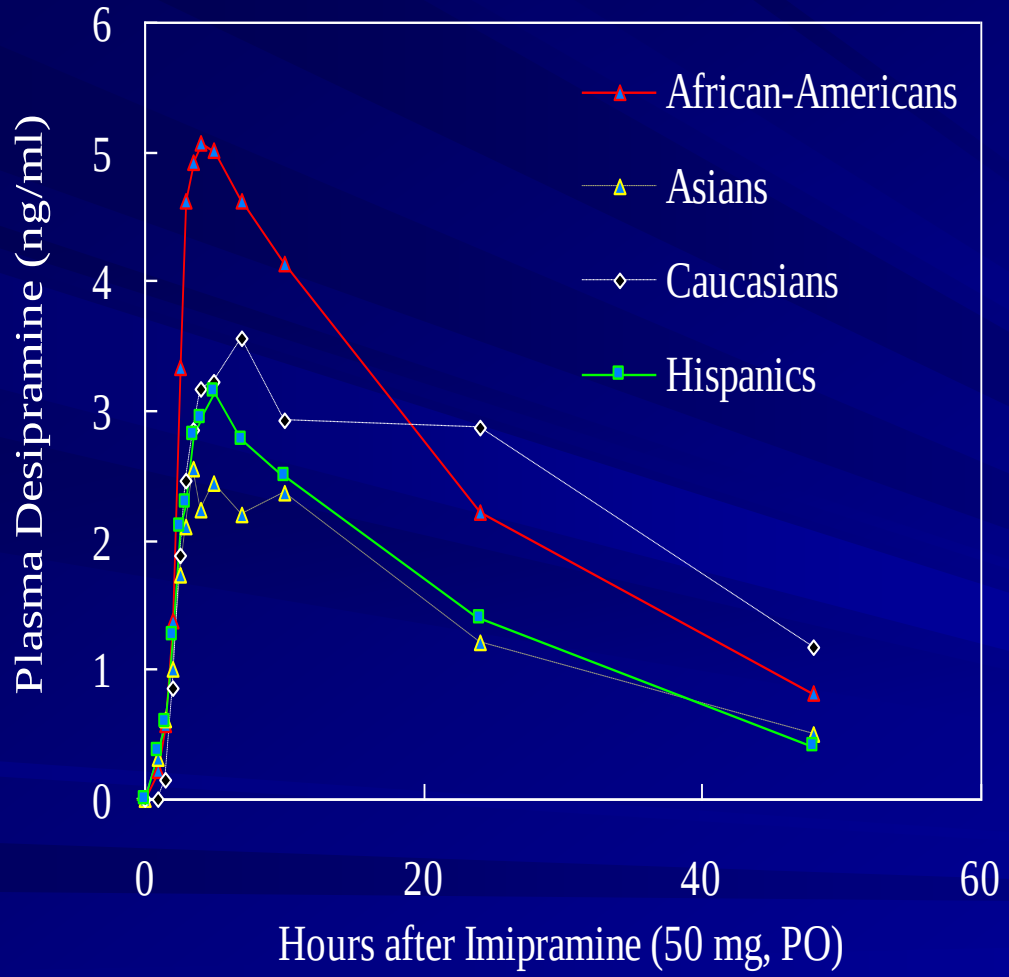
Ethnic Variation in Imipramine Metabolism



Imipramine is metabolized through CYP2D6, CYP2C9 and CYP2C19 into several metabolites; N–oxide of imipramine, OH–imipramine, OH–desipramine, demethyl–desipramine, and desipramine.

Desipramine is then metabolized by CYP2D6. The high levels of desipramine in African Americans is most likely due to the higher rate of CYP2D6 slow metabolizers in this population.

Lin et al, submitted for publication

Hispanic Americans
Antidepressants

- More apt to focus on somatic complaints in depressed
- Lower doses (1/2) of antidepressants
- More anticholinergic side effects
- No difference in pharmacokinetics between Latinos and non-Latino whites

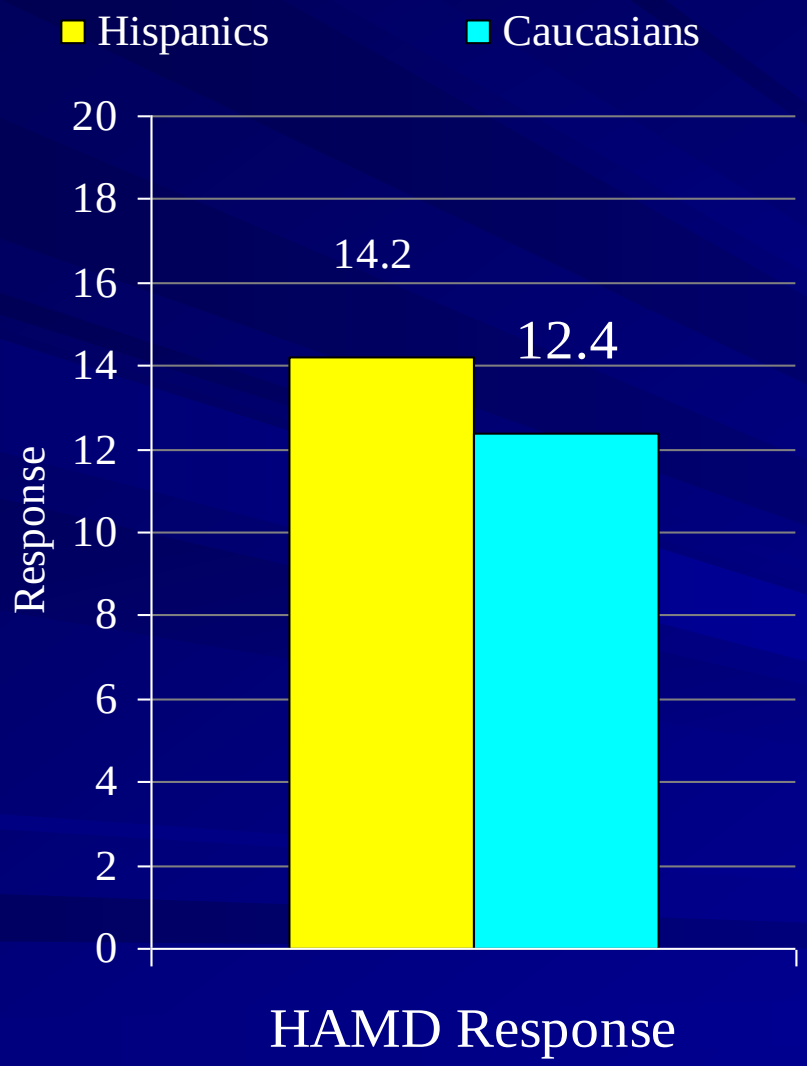
Mezzich & Raab, 1980; Marcos & Cancro, 1982; Escobar & Tuason, 1980; Gaviria et al, 1986 *

Hispanics: Antidepressants
Marcos and Cancro 1982

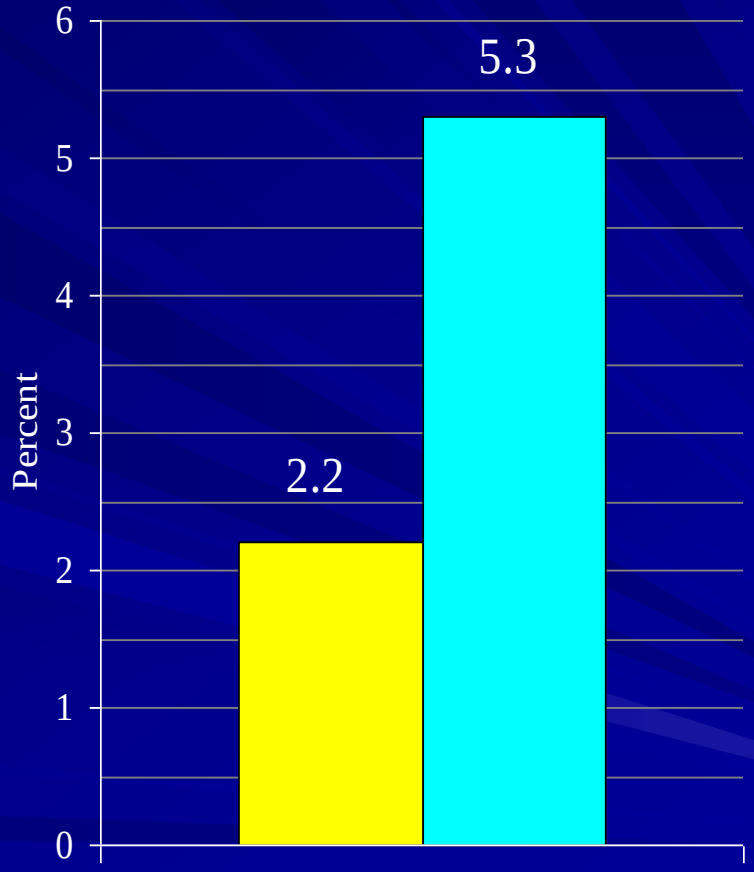
41 Hispanic (PR) and 21 Caucasian female outpatients

- Dosage of TCA (amitriptyline, imipramine, or doxepin)
  - Hispanics 65 mg
  - Caucasians 131 mg
- Percent Response
  - Hispanics 75.6%
  - Caucasians 71.4%
- Side effect profile
  - Hispanics 78 % 17 % discontinued TCA
  - Caucasians 33 % 4.8 % discontinued TCA

Hispanics: Antidepressants
SSRI's: Alonso et al 1997



HAMD Response



Side Effects*

* = P< .005

Asian Americans
Antidepressants

- Asians require lower doses and show a therapeutic response at lower blood levels

Yamashita and Asano 1979; Pi and Gray 1998; Pi et al, 1993

Asian Americans
Antidepressants

- Chinese had higher mean peak plasma levels of both desipramine and the hydroxyl metabolite as well as greater areas under the curve (AUCs) than Caucasians
  - The mean total plasma clearance of desipramine was higher in Caucasian than in Chinese and Show a trimodal distribution of the desipramine clearance
  - Suggested that the differences were under genetic control
- A kinetic study of debrisoquine (a CYP2D6 substrate)
  - Not able to demonstrate a relationship between the metabolism of desipramine and debrisoquine in both Chinese and Caucasian subjects
  - Debrisoquine was cleared rapidly by every subject, including those who were slow clearance in the desipramine study
  - A different enzyme, metabolic pathway, SM's ?

Rudorfer et al, 1984

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Asian Americans
Antidepressants

- Pharmacokinetics of desipramine
  - Asians achieved peak plasma levels in less time (4.0 hours vs. 6.9 hours) than Caucasians
  - No any other pharmacokinetic parameters were found to be statistically significant between the two groups
- A more rigorously designed pharmacokinetic study of desipramine
  - The existence of trimodal distribution of desipramine clearance in both groups
  - The reverse of the previous result was found; the time required to achieve peak plasma levels was shorter (3.0 hours) in Caucasians than in Asians
  - No significant differences in the desipramine saliva-to-plasma ratio between two groups

Pi et al, 1986; Pi et al, 1989; Pi et al, 1991

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Asian Americans
Antidepressants

- Pharmacokinetic study of nortriptyline
  - Japanese subjects achieved higher peak plasma levels and a significantly higher mean AUC than American subjects
  - a greater bioavailability of nortriptyline in the Japanese
- Pharmacokinetic study of clomipramine
  - Asian Indian or Pakistani volunteers had significantly higher mean plasma levels of clomipramine 4 hours after administration of the dose than English volunteers
  - Asian group had higher peak plasma concentrations and more sensitive to advers drug reactions

Kishimoto and Hollister 1984; Allen et al, 1977; Lewis et al, 1980

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African Americans
Benzodiazepines

- Benzodiazepines
  - Less apt to be prescribed
- Pharmacokinetics
  - Increased clearance of adinazolam and decreased clearance of its metabolite.
- Pharmacodynamics
  - More sensitive

Fleishaker & Phillips, 1989

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Asian Americans
Benzodiazepines

- Pharmacokinetic study of diazepam
  - the volume of distribution was lower, and both serum diazepam and desmethyldiazepam levels were higher in Asians than in Caucasians. Due to body fat?

- Asians had higher maximum serum concentrations, large AUCs, and lower clearance of both adinazolam and its major active metabolite than Caucasian and African American counterparts

Ghoneim et al, 1981; Kumana et al, 1987; Ajir et al, 1997

*

Asian Americans
Benzodiazepines

- Greater AUCs and peak plasma concentrations and lower total plasma clearance in both American-born and foreign-born Asian than Caucasian group, after both oral and intravenous administration of alprazolam

- Pharmacodynamically, foreign-born Asians experienced more sedation than Caucasians and American-born Asians

Lin et al, 1988

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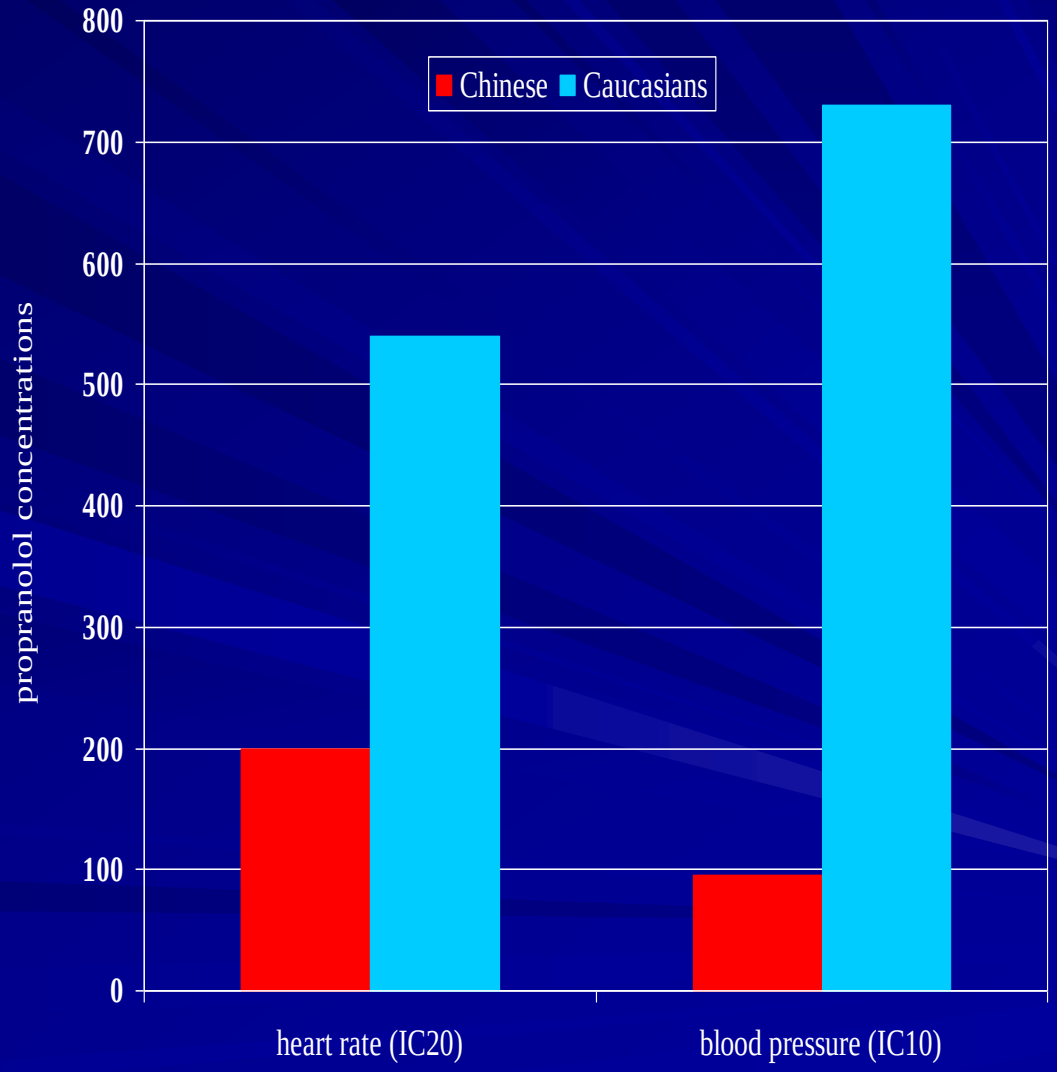
Propranalol Response: Chinese vs. Caucasians

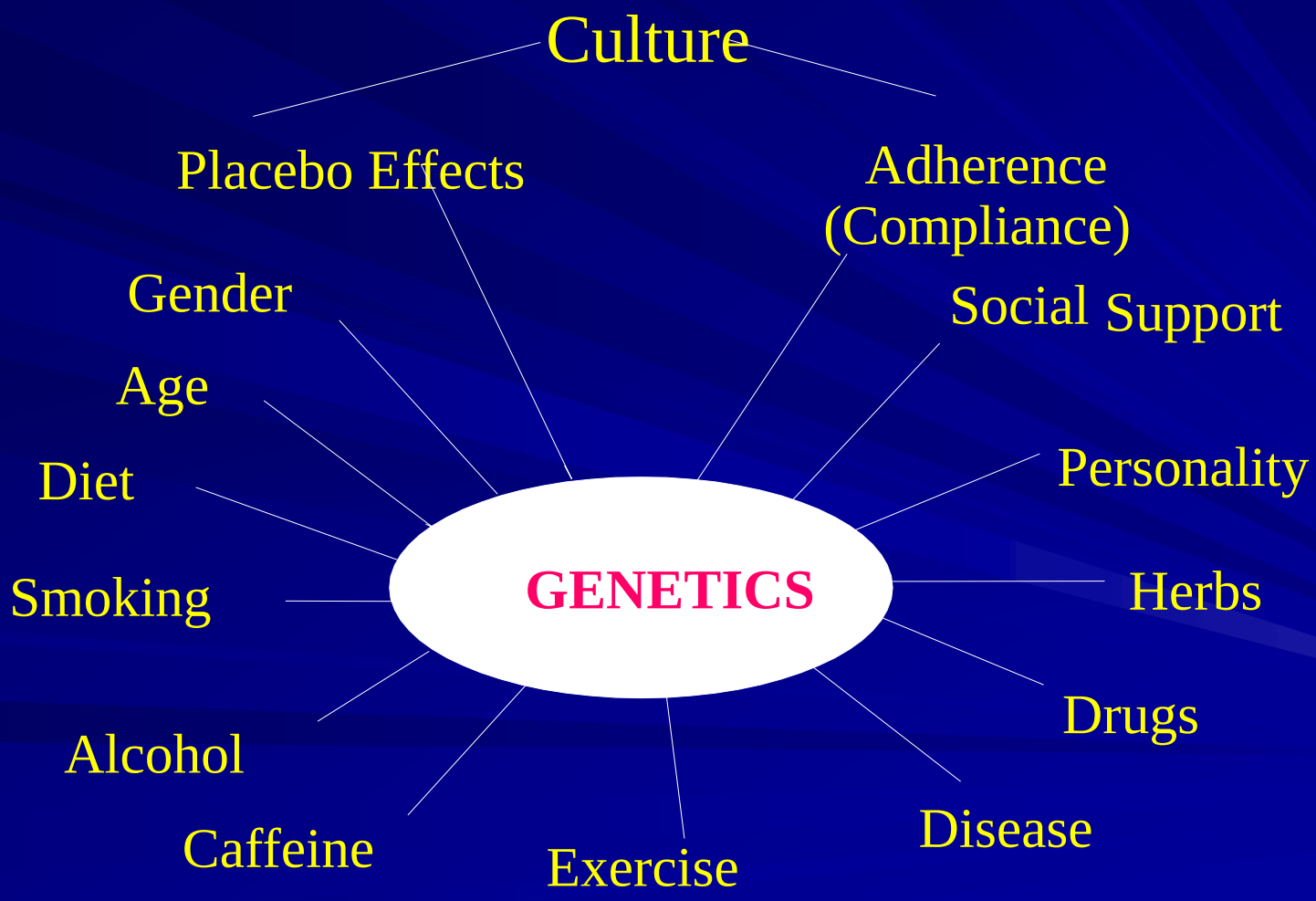
b-blocker propranalol

•Asians require lower doses and experience more effects on blood pressure and heart rate than whites due to b-adrenoceptor sensitivity



Zhou et al, 1989

Factors Affecting Drug Response



Difference in Pharmacokinetics and Pharmacodynamics

- Mainly determined by Genetic Predisposition & Influenced by Patients' compliance, patients' attitude towards pharmacotherapy
- Family members' attitude towards patient expressed emotion (EE) and pharmacotherapy
- Sociocultural issues, environment, societal understanding, demands and tolerance of psychiatric symptoms (STIGMATISM, DISCRIMINATION)
- Physicians' prescribing habits and attitude towards pharmacotherapy
- Costs and availability of medication, facilities, other treatments, support systems, and professionals.

Pi and Simpson, 2005; Dolder et al, 2002; Wang et al, 2002; Phillips et al, 2000; Pi and Gray, 1998 *

Pharmacogenetics

- The study of the relationship between an individual's genotype and his/her ability to metabolize particular pharmacological compounds
- Pharmacogenetic profile can influence both the pharmacokinetics and the pharmacodynamics of a given medication

Pharmacodynamics

- The effects of a drug on the body such as tissue or receptor sensitivity
- Explains some ethnic differences in therapeutic doses/effects and side effects of various psychotropic medications

Pharmacokinetics

The way in which the body handles drugs

- Absorption
- Distribution
- Metabolism (Biotransformation)
- Excretion (Elimination)

Plasma Proteins

- Plasma concentrations of **a_1-acid glycoprotein**,
  - a plasma protein that provides binding sites for psychotropic drugs in the blood, significantly **lower** in Asians than in whites and African Americans

Zhou et al, 1990

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Acetylation

- Acetylation enzyme polymorphism
- The majority (78%-93%) of Chinese and East Asians are fast acetylators
- Only 50% of whites and African Americans are fast acetylators
- Caffeine, clonazepam, nitrazepam, and phenelzine are metabolized through acetylation

Weber 1987; Sjoqvist et al, 1997

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Conjugating enzymes (transferases)

- Genetically determined
- Can also be induced by various environmental factors:
  - alcohol, coffee, oral contraceptives, diet, and tobacco
- The clearance of acetaminophen (85%-90% excreted after glucuronide or sulfate conjugation), 20% slower in Asians than in Europeans

Mucklow et al, 1980

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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

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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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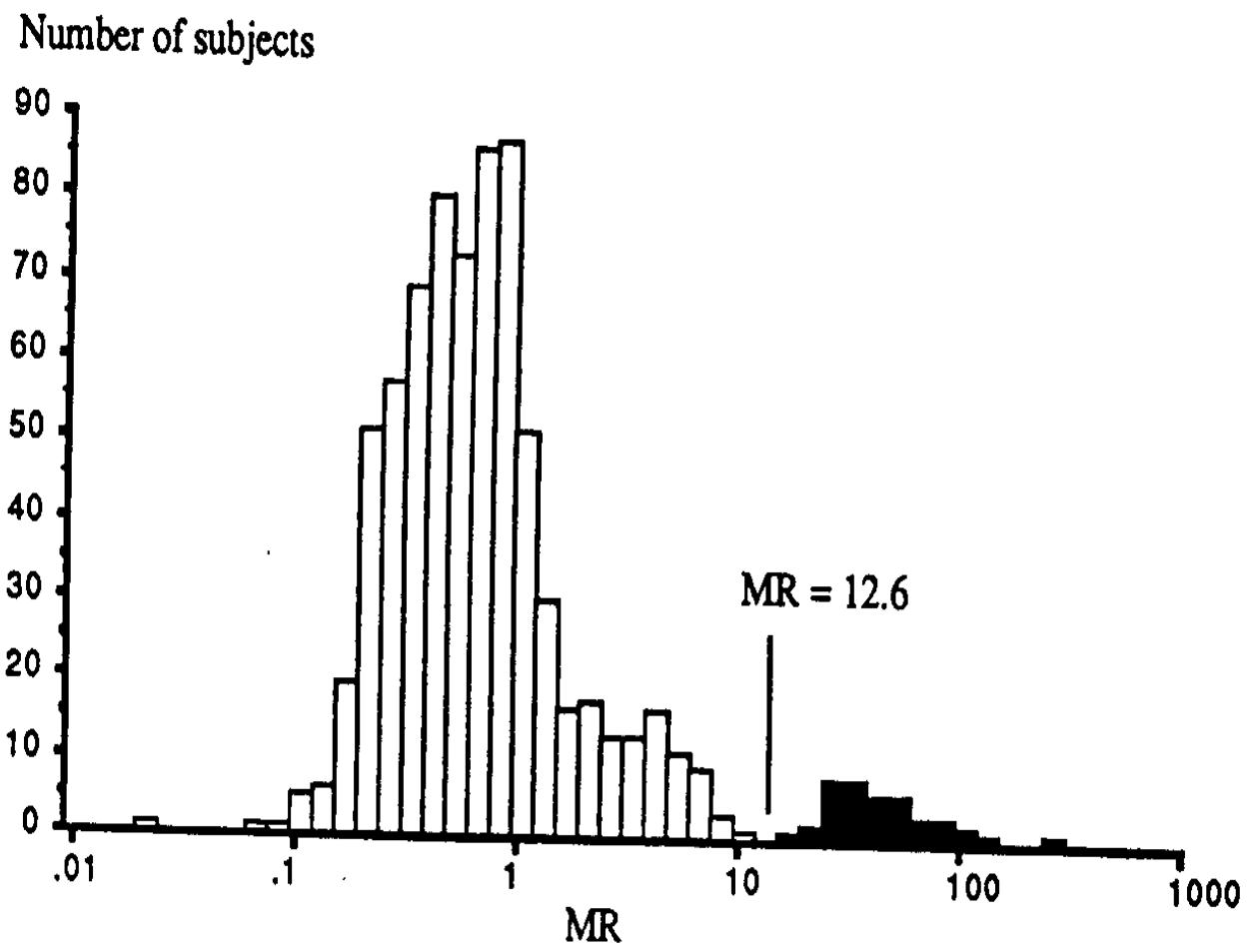
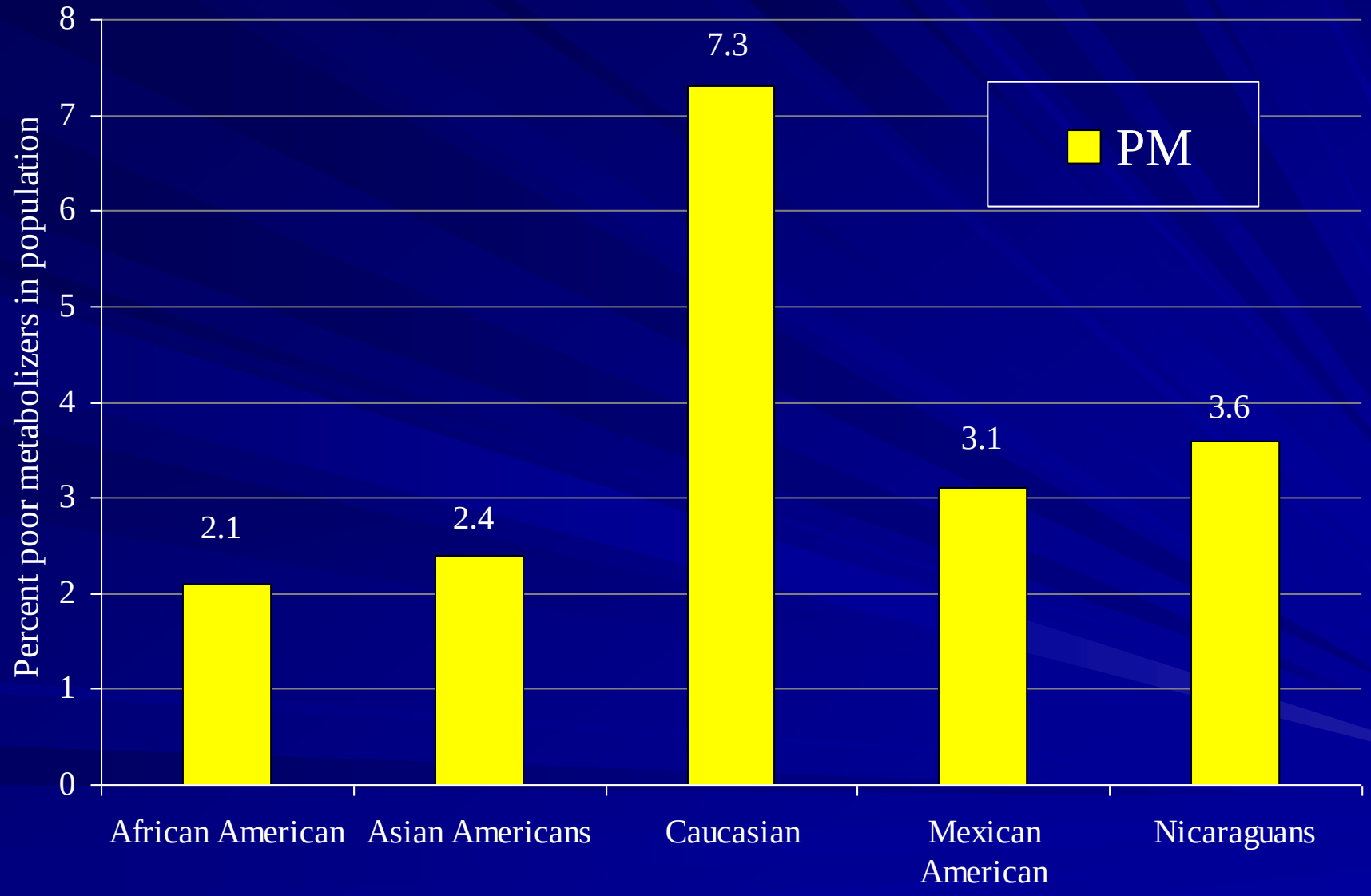
Distribution of CYP2D6 Activity in Caucasian Populations



CYP2D6 Poor Metabolizers



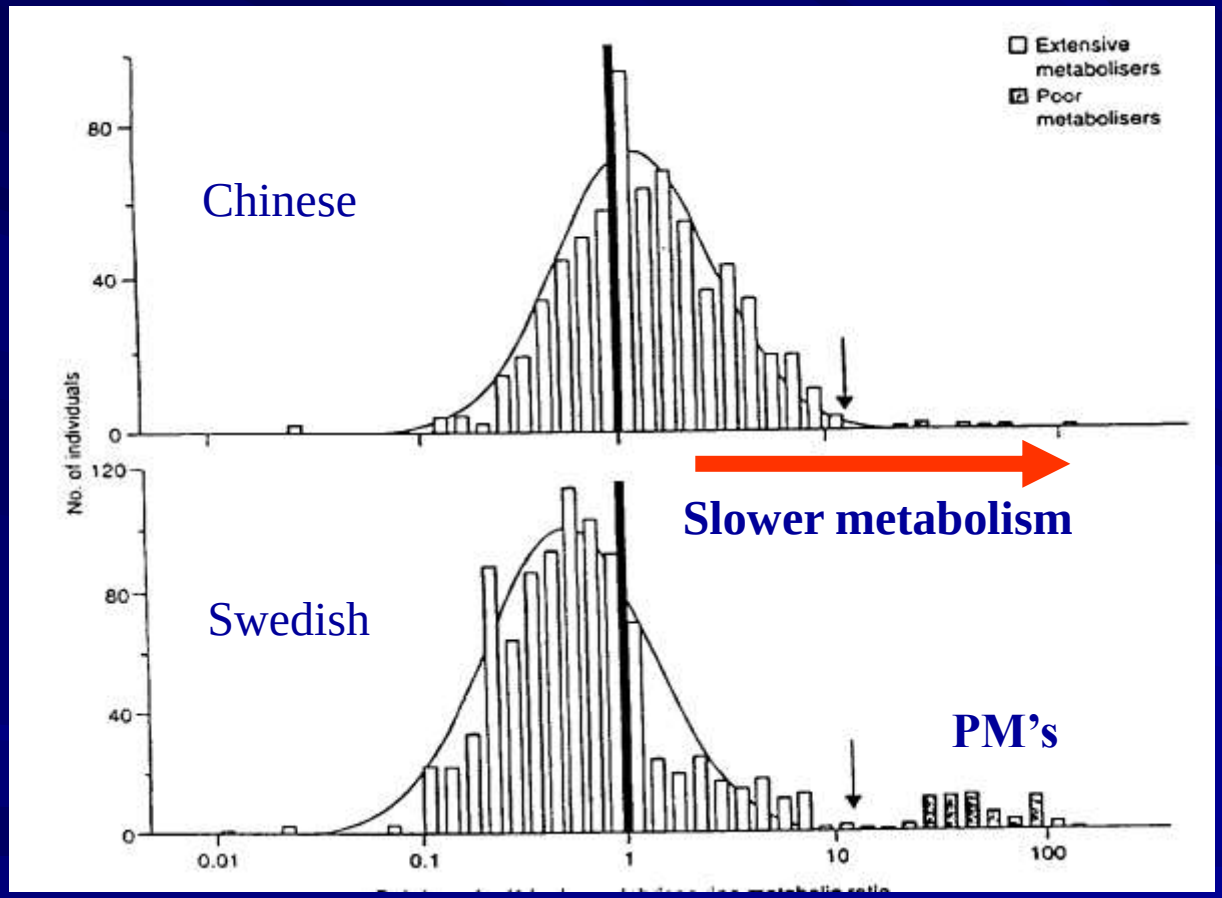
Adapted from Smith 2005

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

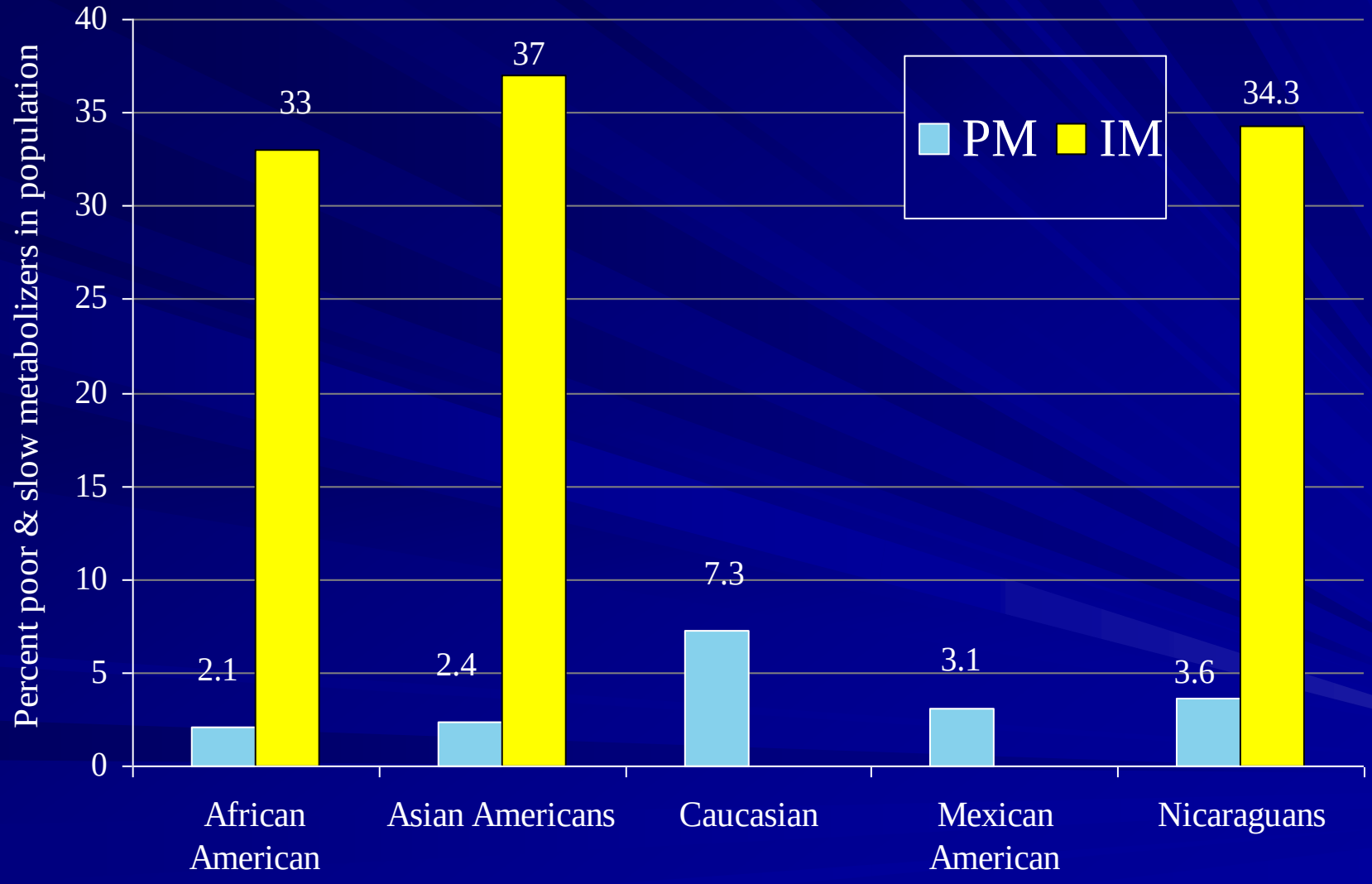
Histograms of CYP2D6 activity in Chinese and Swedish Caucasians display variations in activity. Although Chinese display lower PM rates, they display lower overall metabolic activity due in part to higher rates of IM's

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

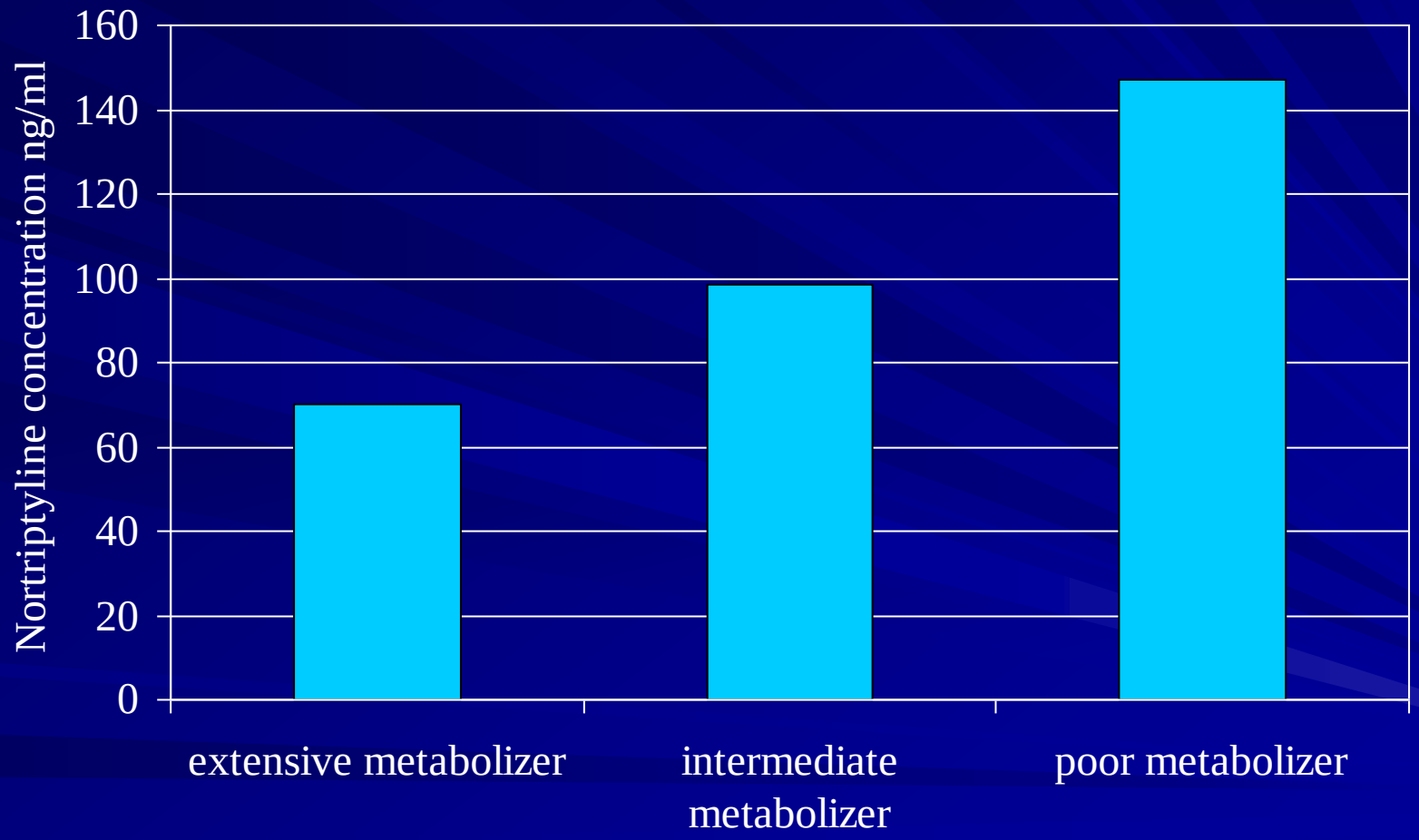
Adapted from Smith 2005

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.

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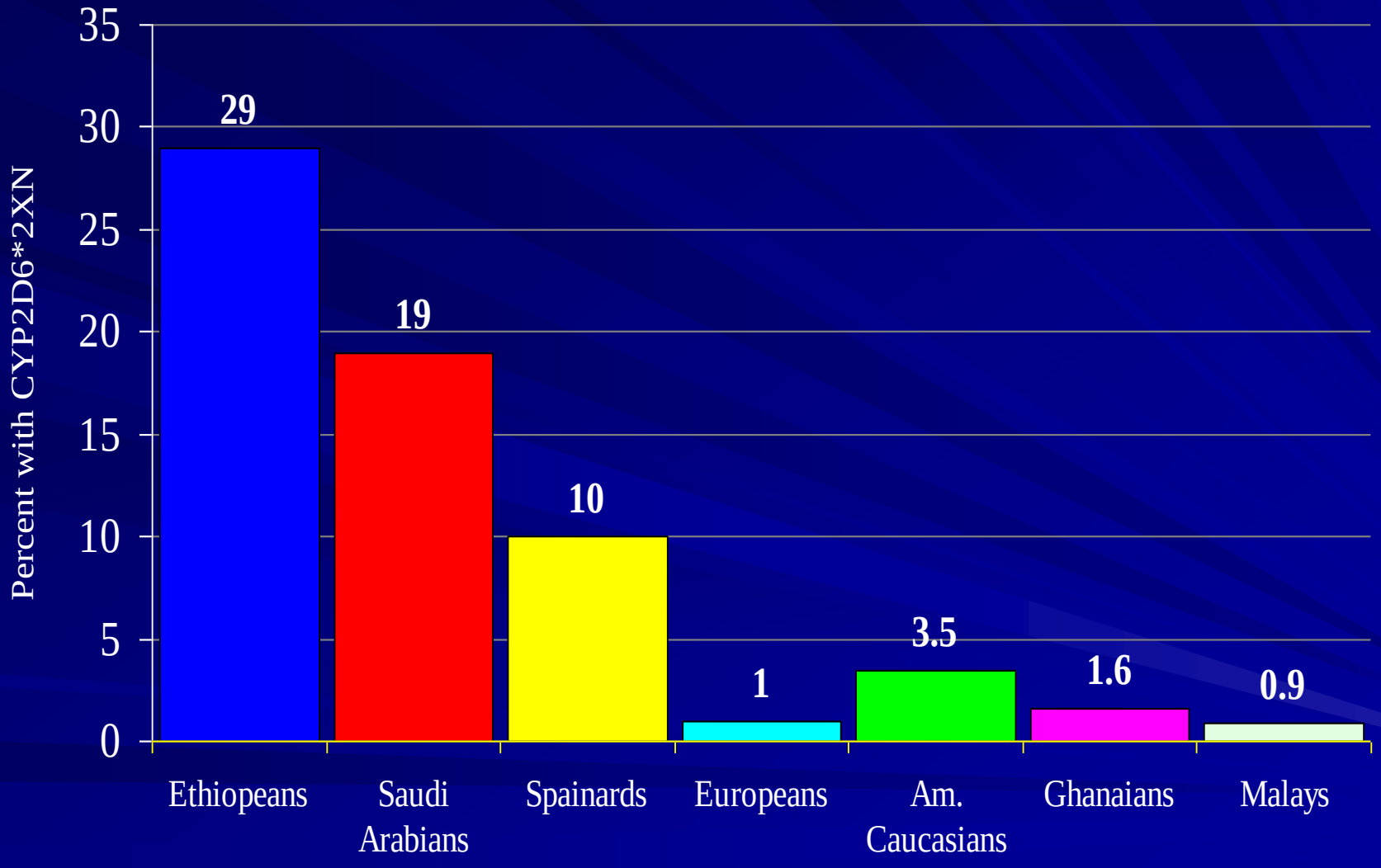
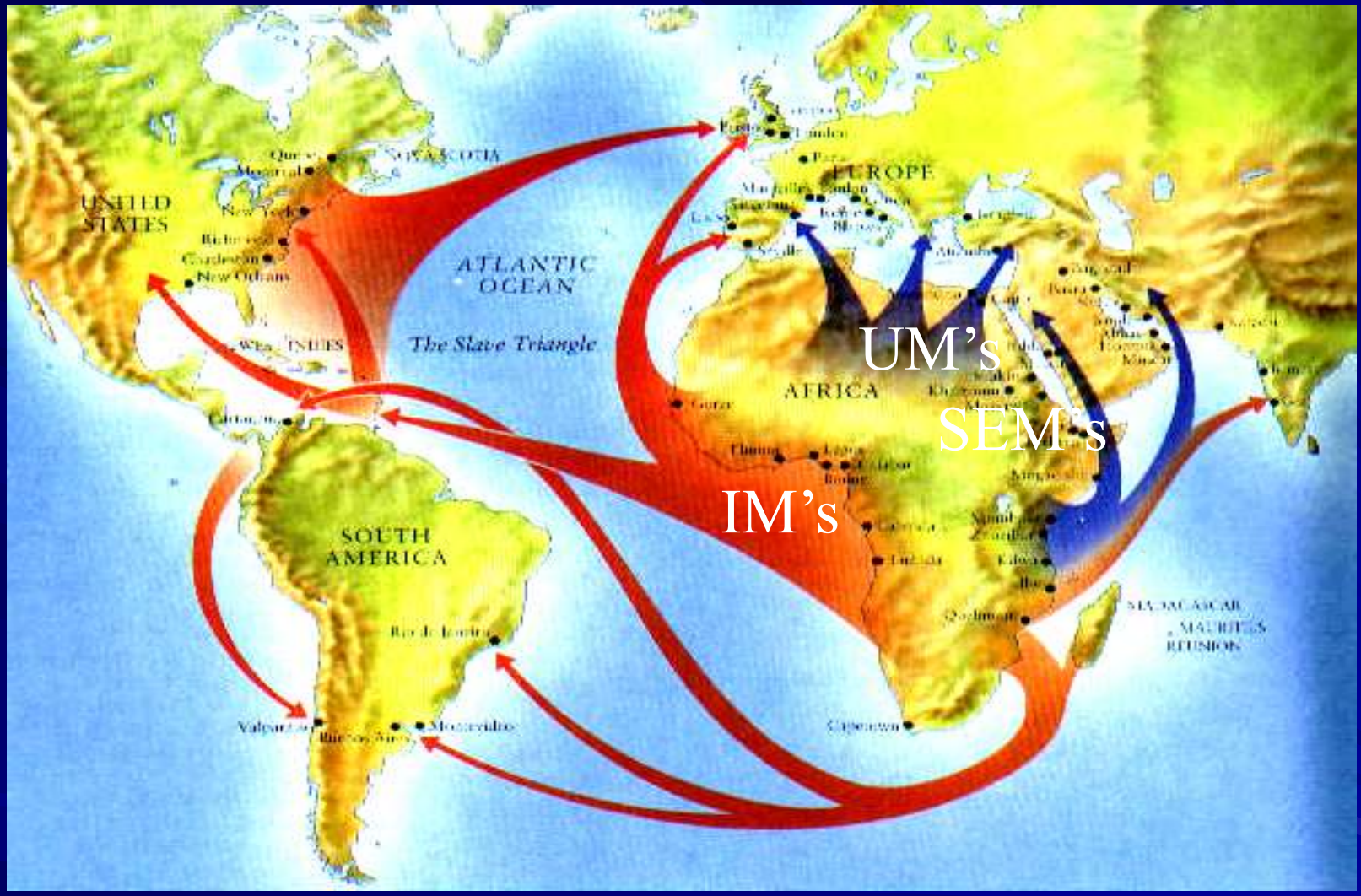
CYP2D6 Ultra Metabolizers



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

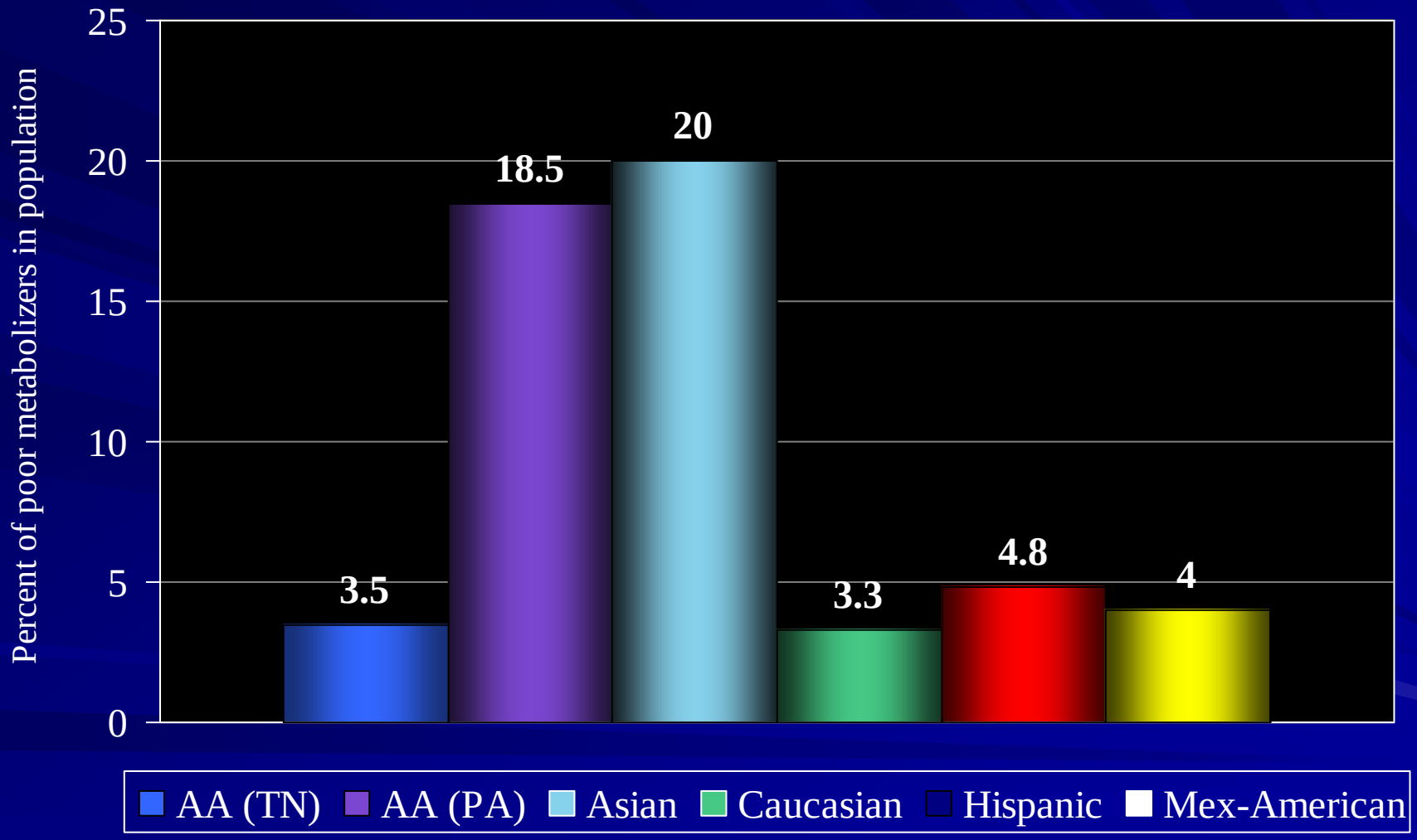
- propranolol, hexobarbital, mephobarbital
- proguanil, omeprazole, S-mephenytoin

*partial route of metabolism

adapted from Smith 2005

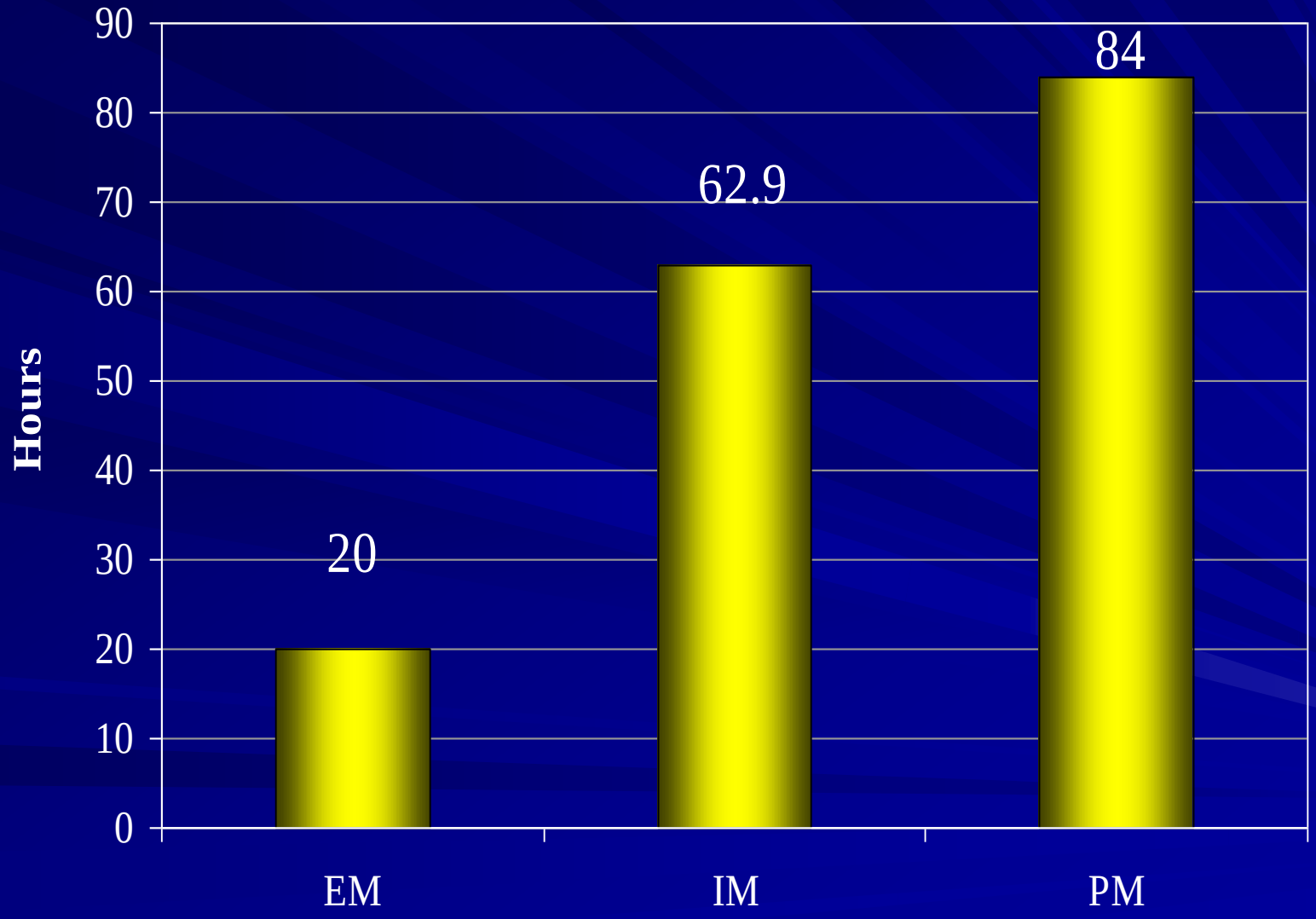
*

Poor Metabolizers (PM) of CYP2C19



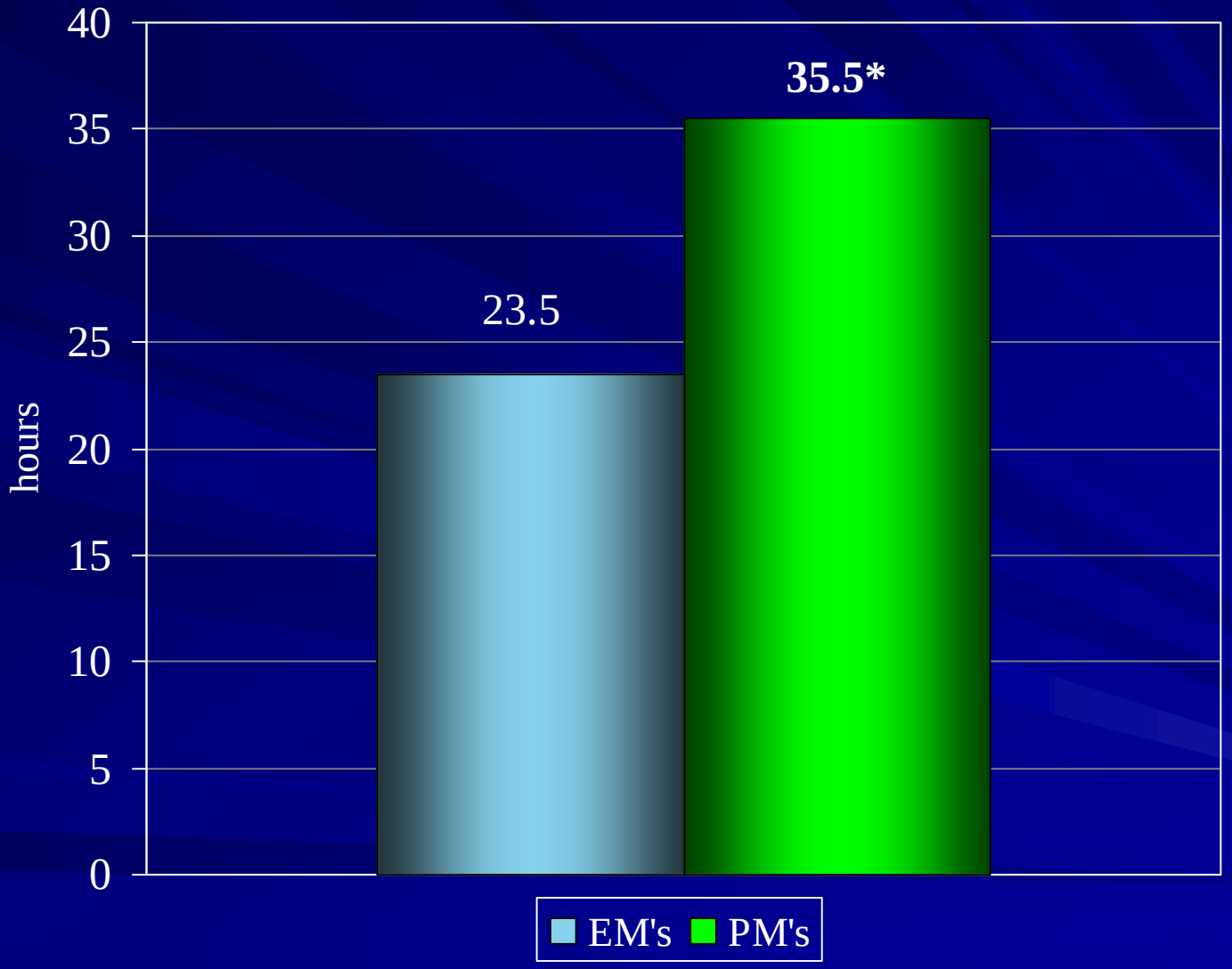
adapted from Smith 2005

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

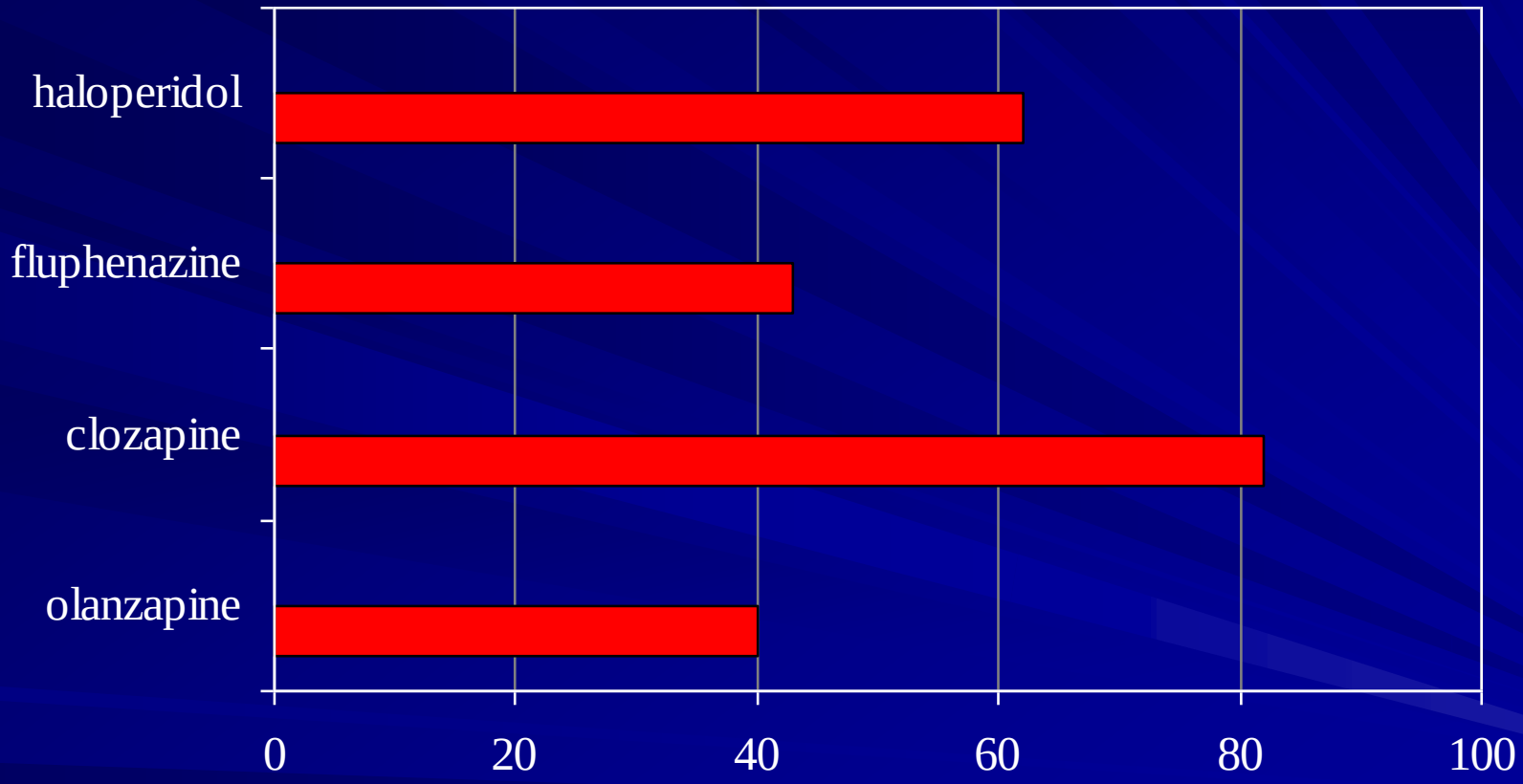
*

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

*

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

*

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

*

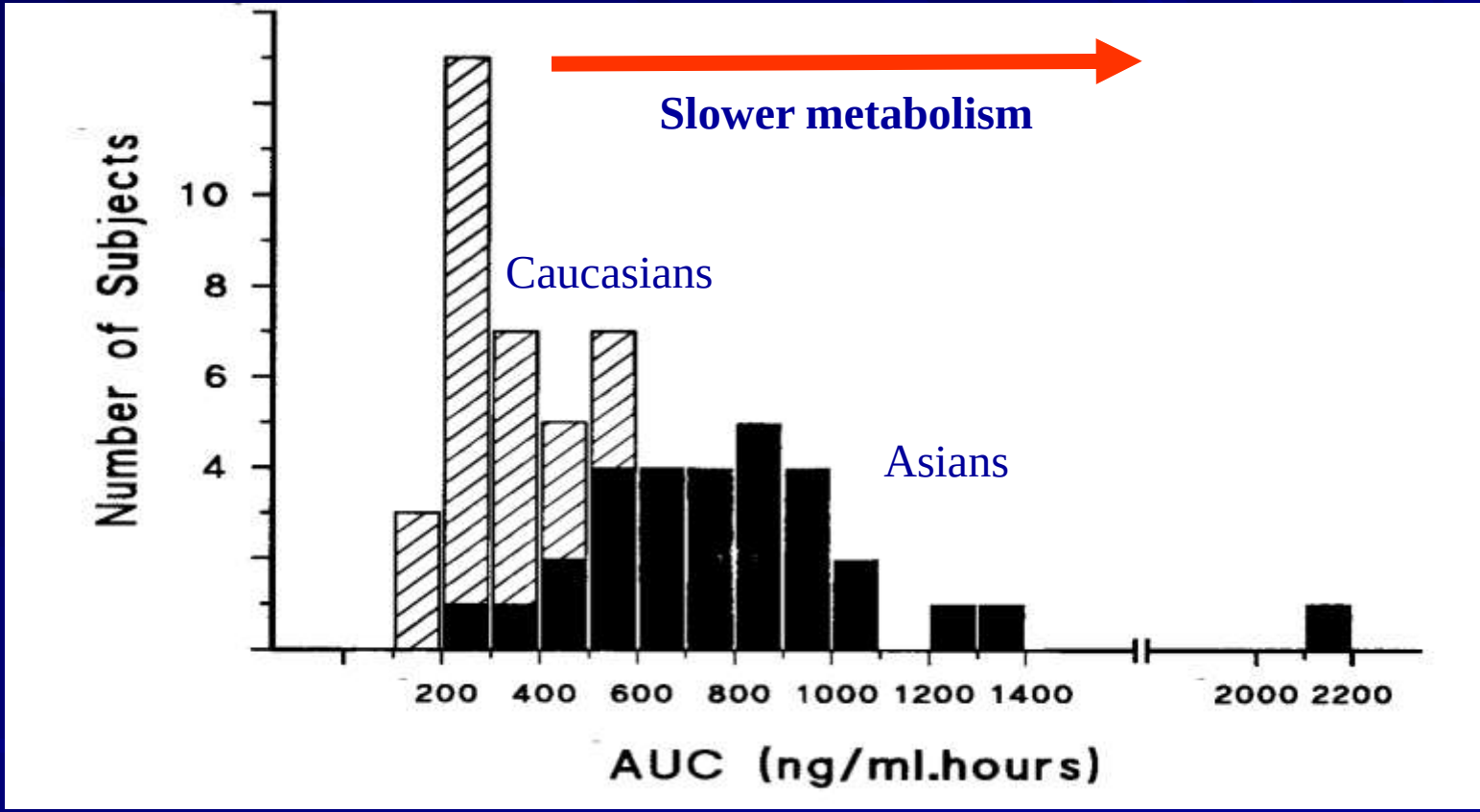
CYP3A4 Inhibitors & Inducers

- 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

*

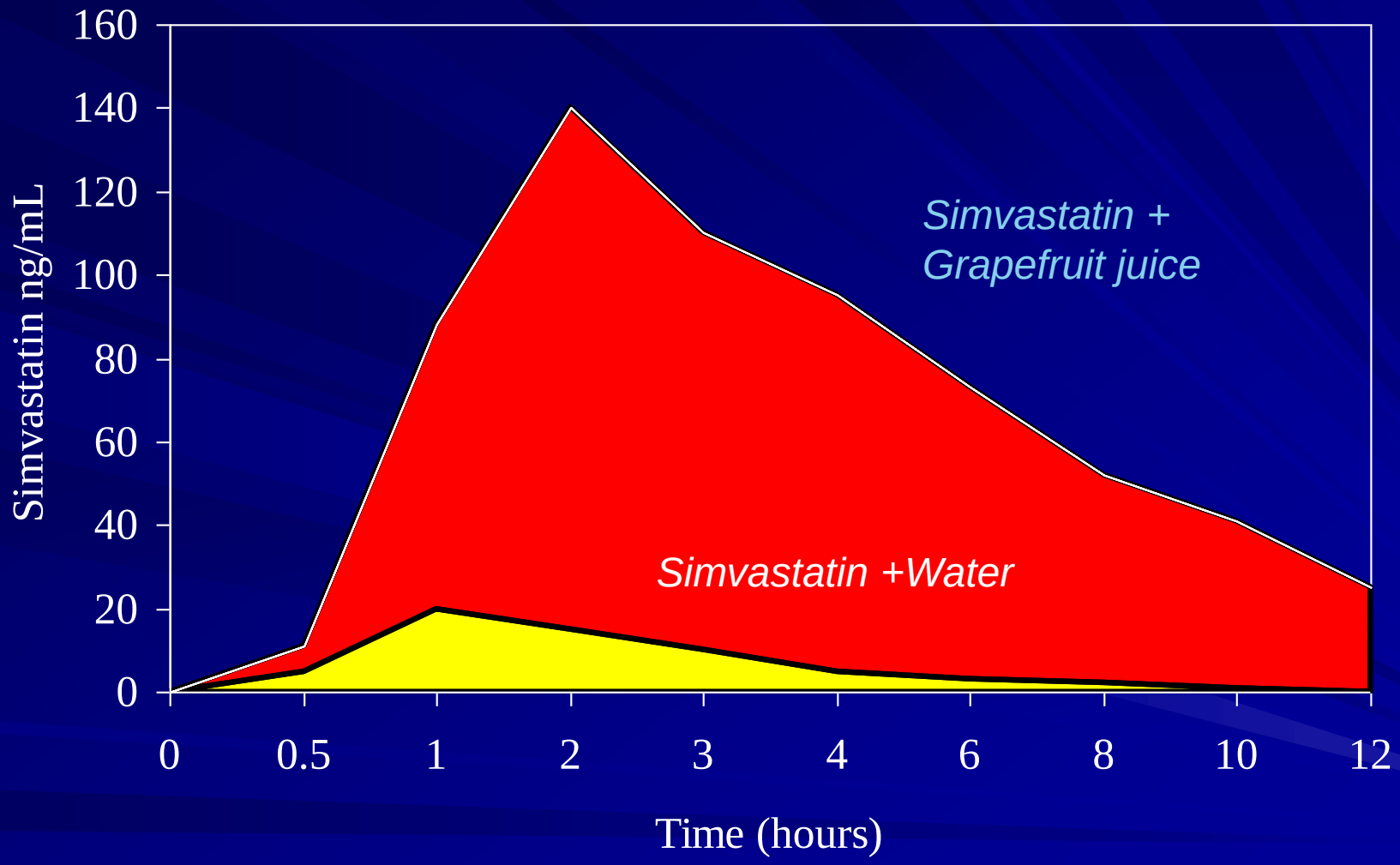
Nifedipine Metabolism in Asian Indians and British Caucasians



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

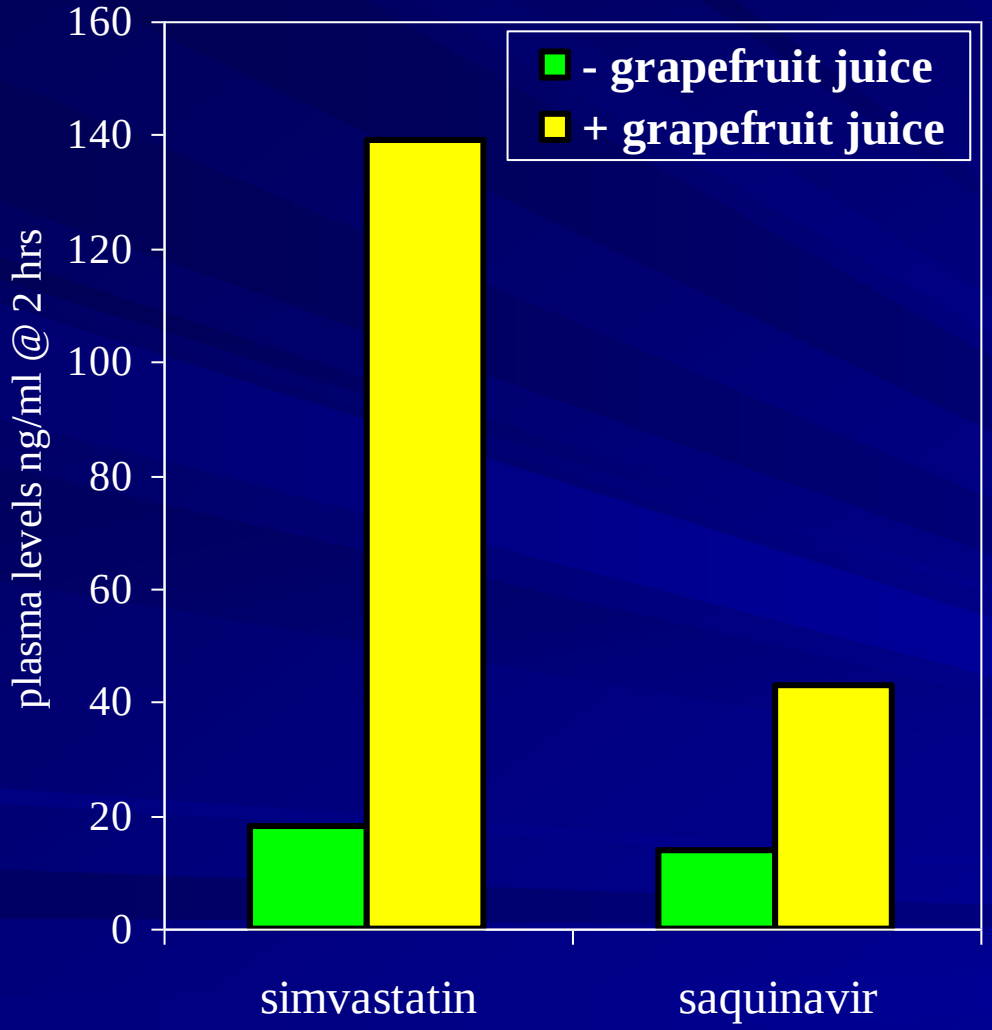
Sowunmi et al, 1995

Simvastatin/Grapefruit Juice



Lilja et al, 1998

Grapefruit Juice Inhibits the Metabolism of Simvastatin and Saquinavir



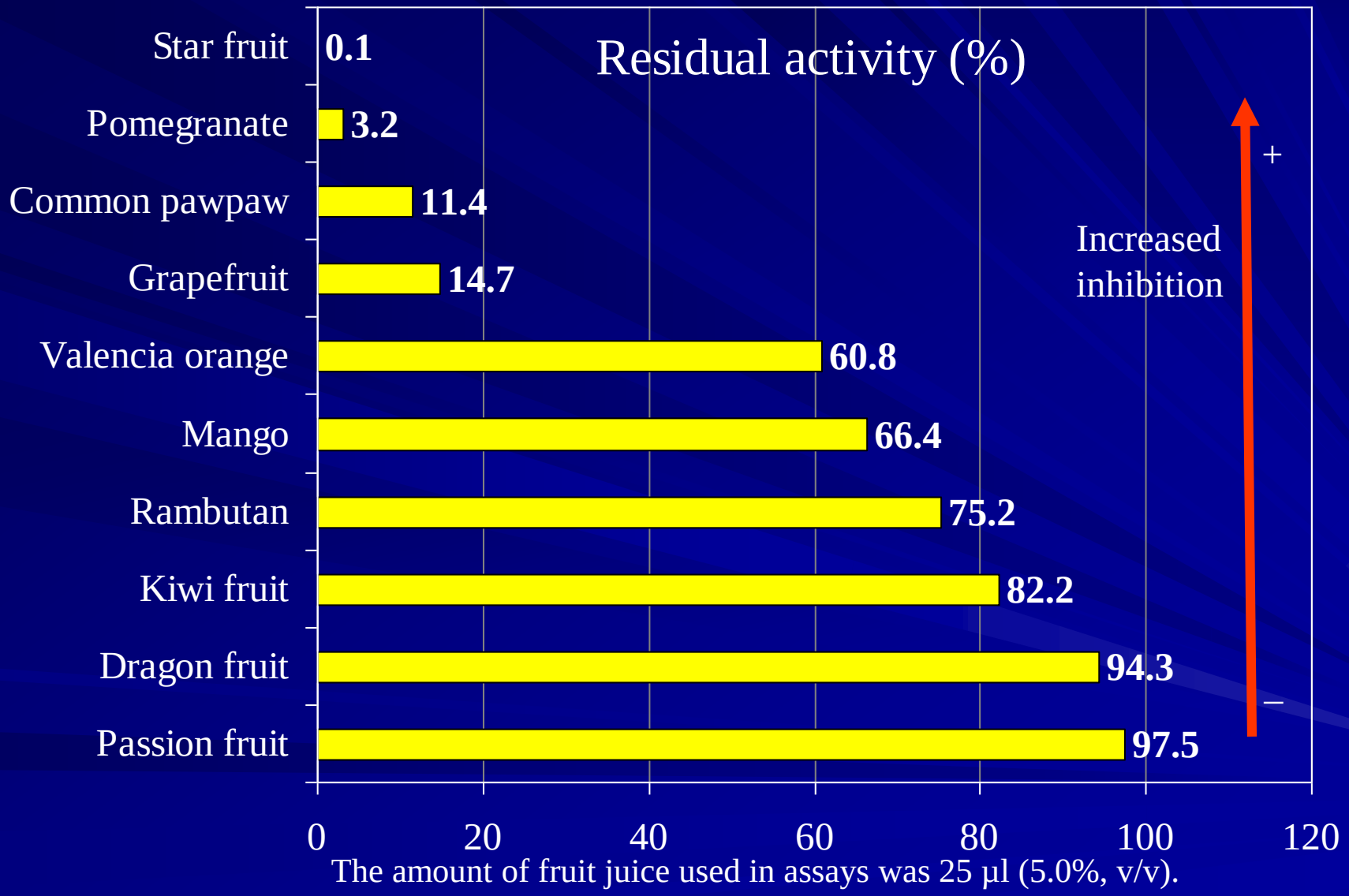
Grapefruit juice is a strong inhibitor of CYP3A4.
It inhibits the enzyme in the small intestine which allows more drug to be absorbed into the bloodstream.

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

*

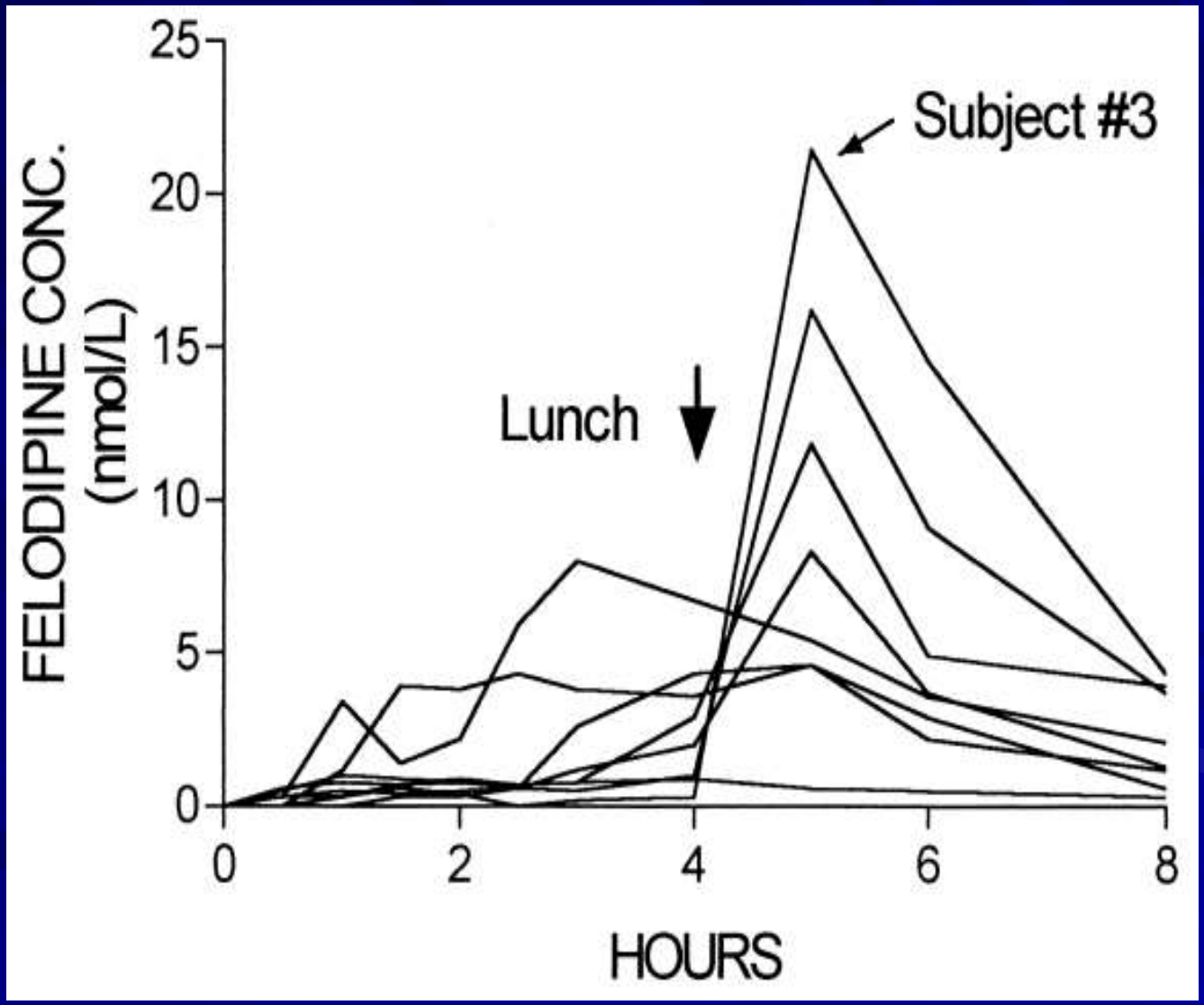
Effects of Tropical Fruit Juice on In-vitro CYP3A4 Activity



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

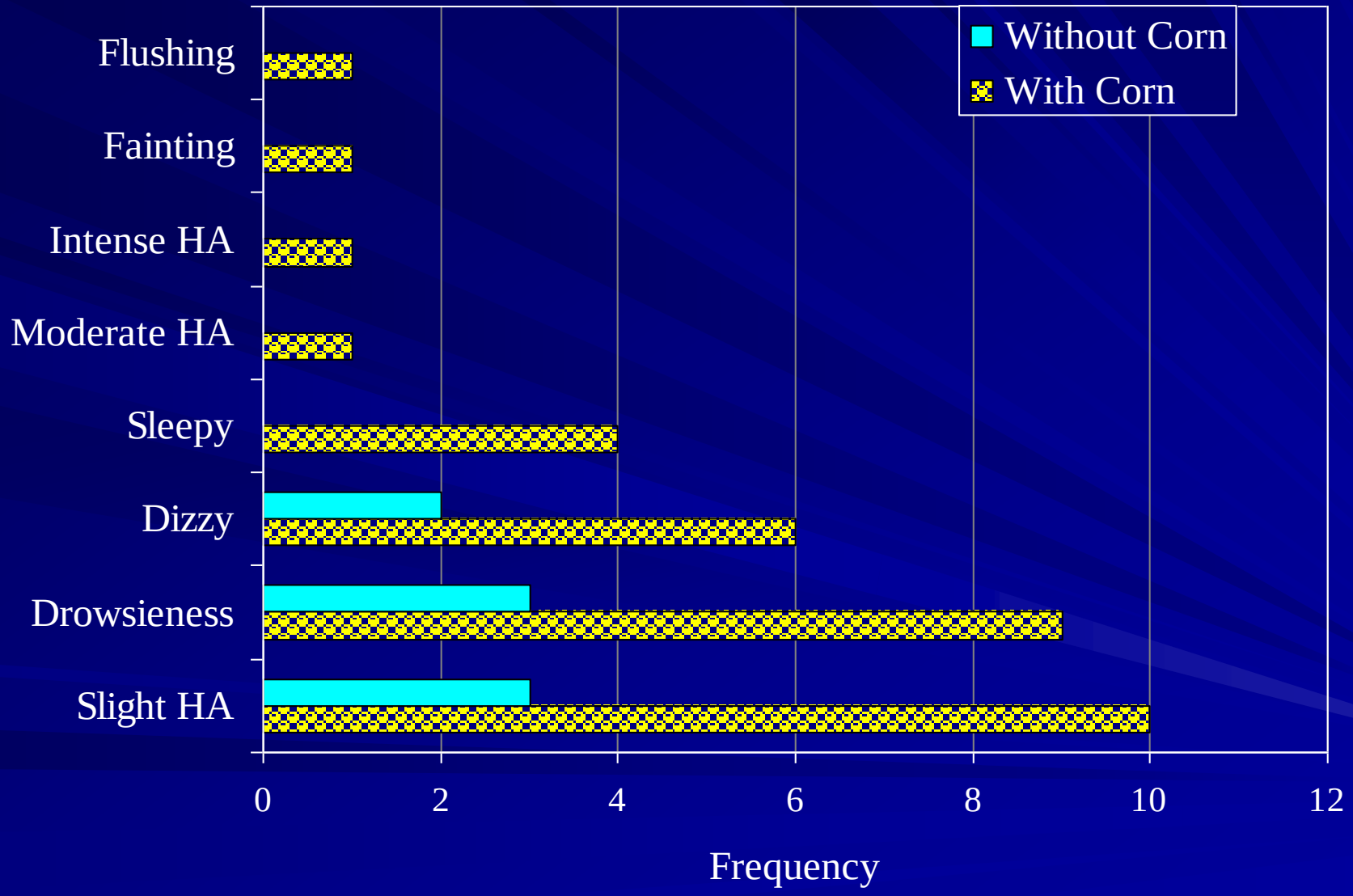
Hidaka et al, Drug Metab Dispos. 2004

Felodipine, & Cabernet Sauvignon



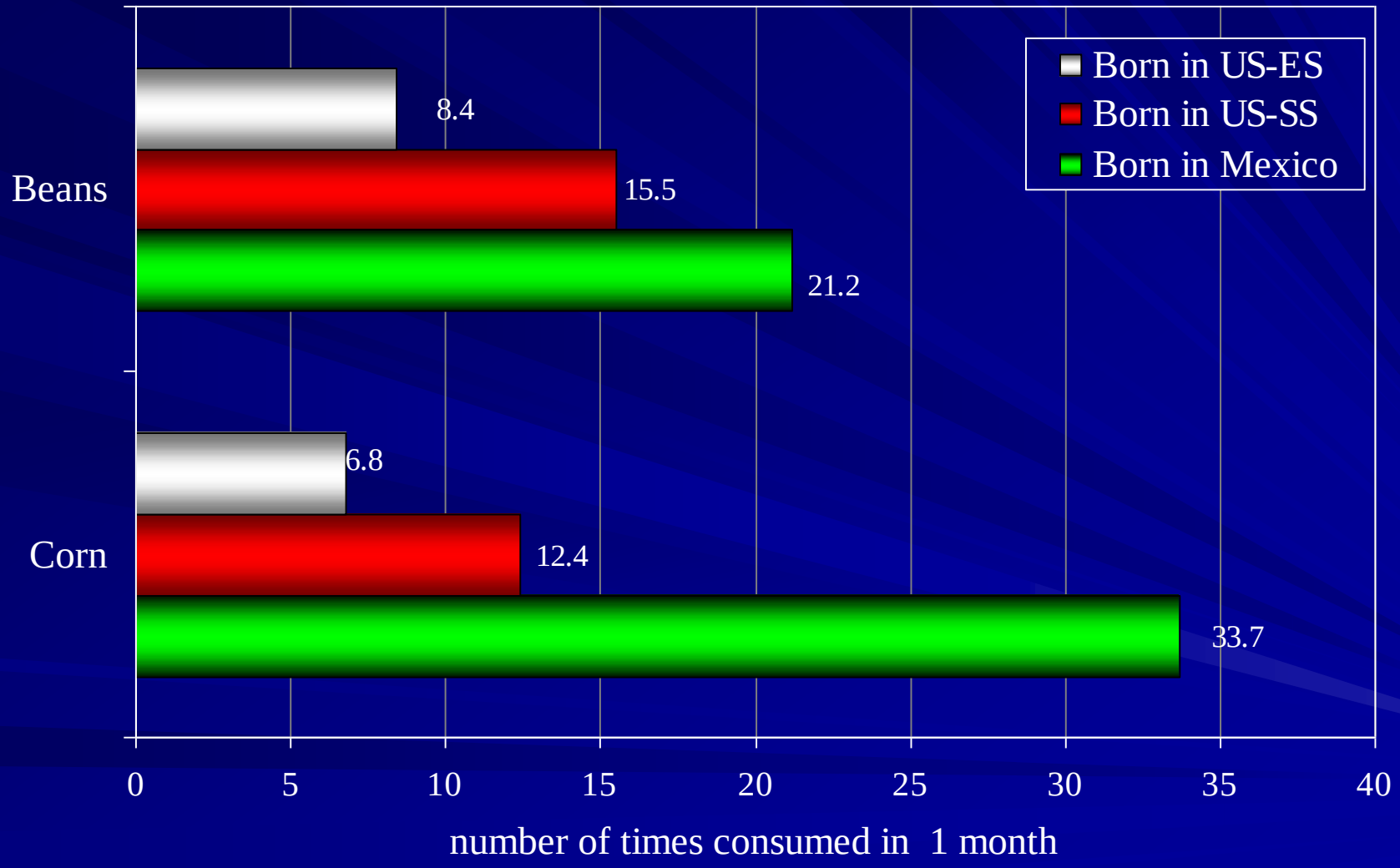
Bailey et al, 2003

Nifedipine Side Effects and Corn



Palma-Aguire, 1999

Diet Variation, Migration & Acculturation Among Mexican American Women



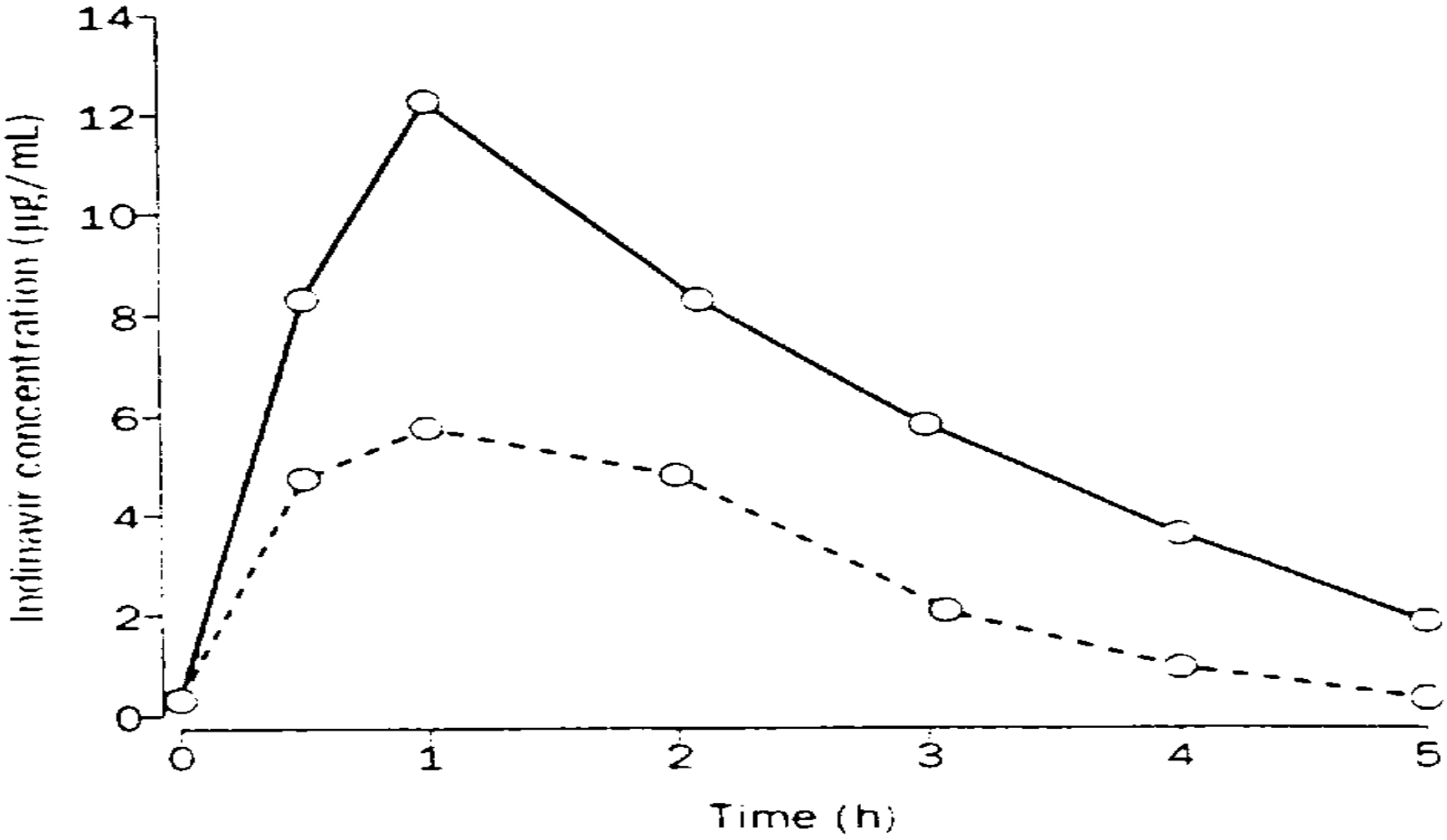
Dixon et al, 2000

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

Recommendations and Conclusions

- 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

*

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

Post-lecture Examination Question 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 Question 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 Question 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 Question 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 Question 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

Answers to Pre & Post Lecture Exams

1. D
2. D
3. D
4. D
5. A

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