CROSS-CULTURAL PSYCHOPHARMACOLOGY

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This slide presentation is a memorial of

Dr. Michael W. Smith

for his dedication and contribution to the research in this field

Major Teaching Points

- Understand the importance of cross-culture perspective in providing psychiatric care for our ethnic diversified society.
- Literature reviews of pharmacological profiles of major ethnic minority groups in USA, ie. African-American, Hispanic-America, Asian-American, American Indian, etc. as comparison to Caucasian counterpart.
- Highlight the ethnic considerations of major psychotropic medication classes, ie. Antipsychotics, antidepressants, mood stabilizers, benzodiazapine, etc.
- Apply integrative approach in which biological, ethnic, and cultural diversity are taking into account and treatment is tailored to specific individual characteristics.

Outline of Presentation

- Introduction
- Clinical studies demonstrating ethnic variations in metabolism and response
  a. Antipsychotics
  b. Lithium
  c. Antidepressants
  d. Benzodiazepines
- Mechanisms for Ethnic variations
  a. Pharmacological: protein binding, metabolism, etc.
  b. Drug metabolizing enzymes:

     CYP 2D6

     1. Introduction
     2. Substrates and inhibitors
     3. Ethnic frequency of poor metabolizers (PM), intermediate metabolizers (IM), and ultra metabolizers (UM)
     4. Clinical implications of PM, IM, and UM status (i.e. PM require low dosage and develop more side effects, UM's may require high dosage for response, etc)

Outline of Presentation (con't)

b. Drug metabolizing enzymes:

CYP 1A2

1. Introduction
2. Substrates, inhibitors and inducers
3. Ethnic variation
4. Clinical implications of induction and inhibition

CYP 3A4

1. Introduction
2. Substrates, inhibitors and inducers
3. Ethnic variation
4. Clinical implications of induction and inhibition

- Summary

Pre-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

Pre-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

Pre-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

Pre-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, African Americans and Hispanic Americans. They 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 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

Cross-cultural Psychopharmacology

- A branch of science seeks to determine whether differences exist between ethnic groups in their response to psychotropic medications, 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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Definitions

- Culture: an integrated pattern of human knowledge, belief, and behavior characteristic of a particular social, ethnic, or age group

- Ethnicity: a group of people whose members identify with each other, through a common heritage, often consisting of a common language, a common culture and/or an ideology that stresses common ancestry.

- Race: distinct genetically divergent populations within the same species with relatively small morphological and genetic differences.

Asian Culture and Attitudes Toward Mental Illness

- Asian Americans are Americans of Asian descent. The U.S. Census Bureau defines Asian as a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Indonesia, Japan, Korea, Malaysia, Bangladesh, Pakistan, the Philippine Islands, Thailand, and Vietnam.
- Linguistically and culturally heterogeneous
- Mental disorders are 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 to 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

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
- The treatment outcomes of Spanish-speaking Hispanic are different from that of English-speaking counter part in STAR*D trial.

Collazo et al, & Ruiz et al, 1996; Ramirez, 1996; Jann et al, 1993; Carno et al, 1969; Trevino & Rendon, 1994; Lesser et al 2008

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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
- Recent analyses of STAR*D trial indicate that African-Americans have similar treatment outcomes for depression compared to those of Caucasians, suggesting that the measurement-based care can reduce ethnic differences.

Sramek et al, 1991; Glazer et al,1994; Jeste et al, 1995; Lesser et al 2010

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American Indians and Alaska Natives

- Culturally heterogeneous, classified into distinct regions and tribes
- The population is remarkably young, with median age of 20.4 for American Indians and 17.9 for Alaska natives
- Economically impoverished, high unemployment rates, high arrest rates, lowest years of education
- High prevalence of alcohol and drug abuse and dependence; Alcohol abuse is among the leading cause of death;
- High rates of depression and high incidence of suicide
- Many traditional healing practice

Manson, et al, 1987

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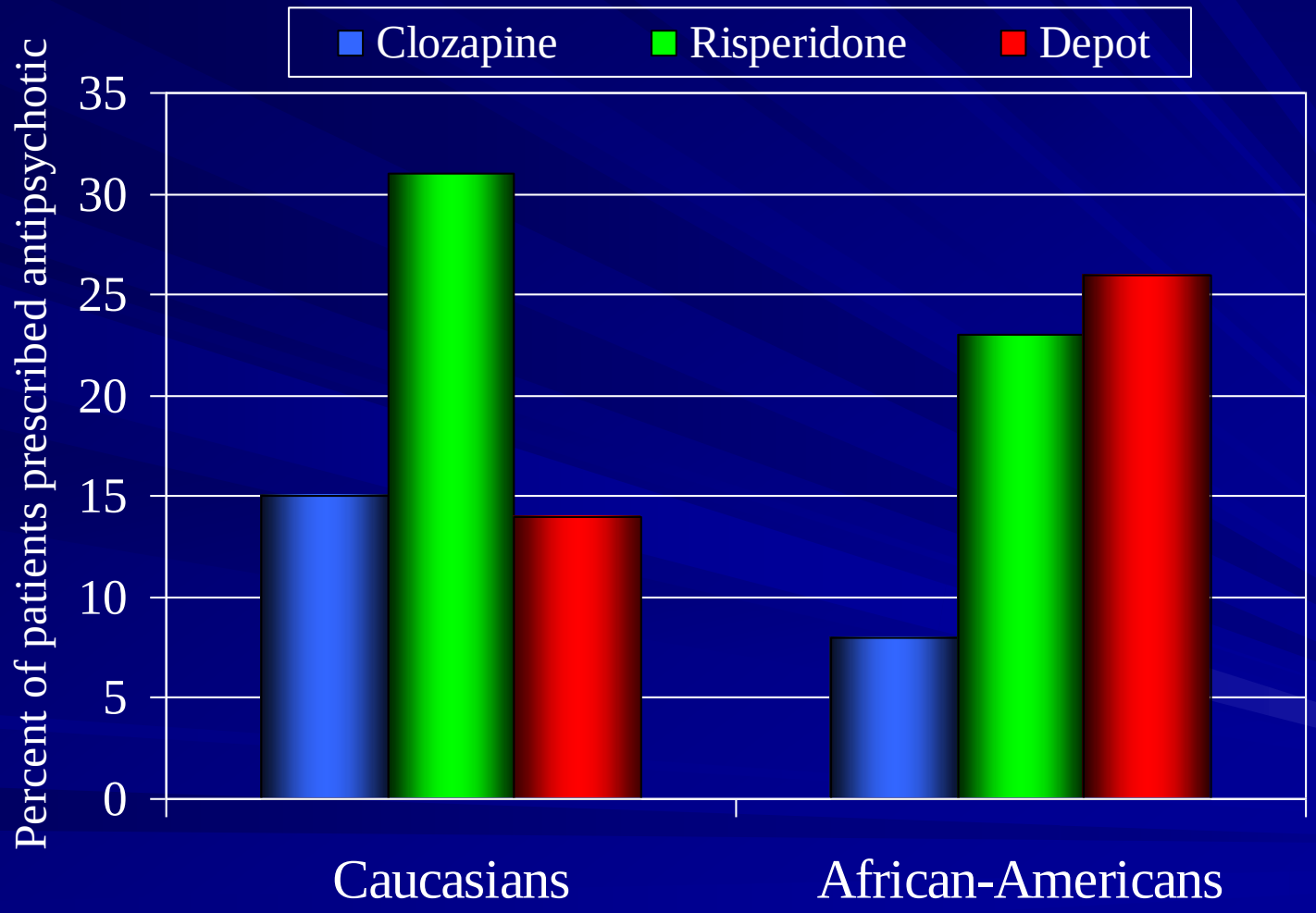
Racial Disparities in Antipsychotic Prescription Patterns



Kuno & Rothbard, 2002

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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

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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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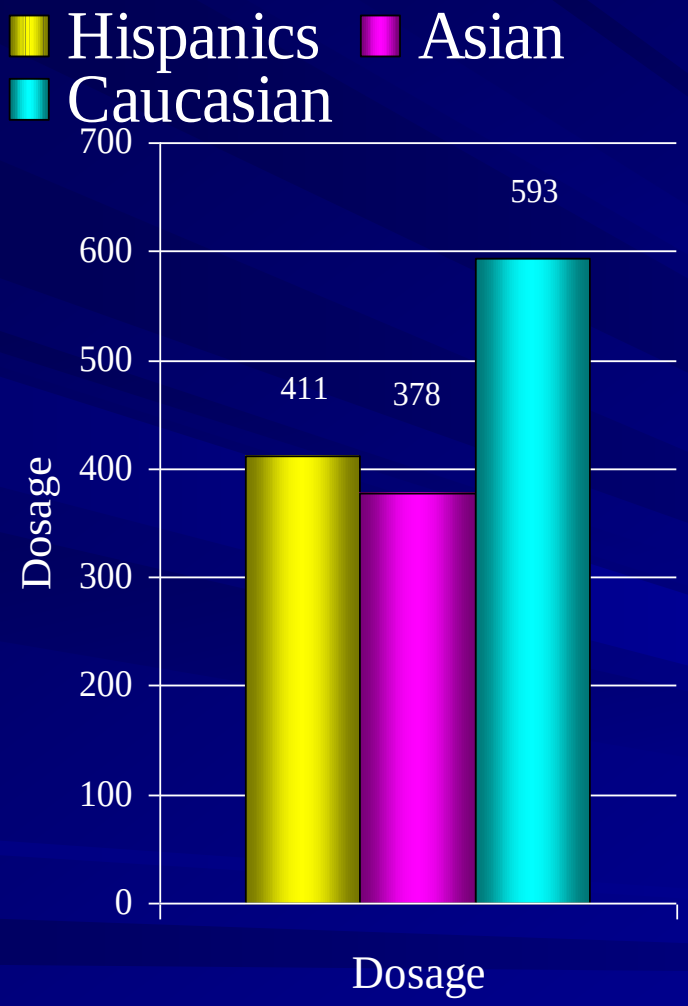
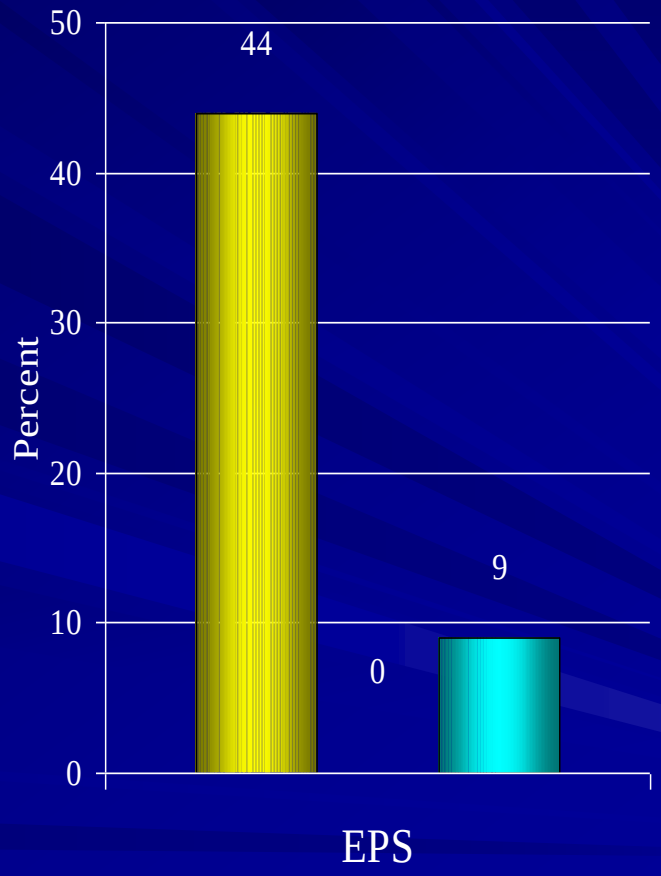
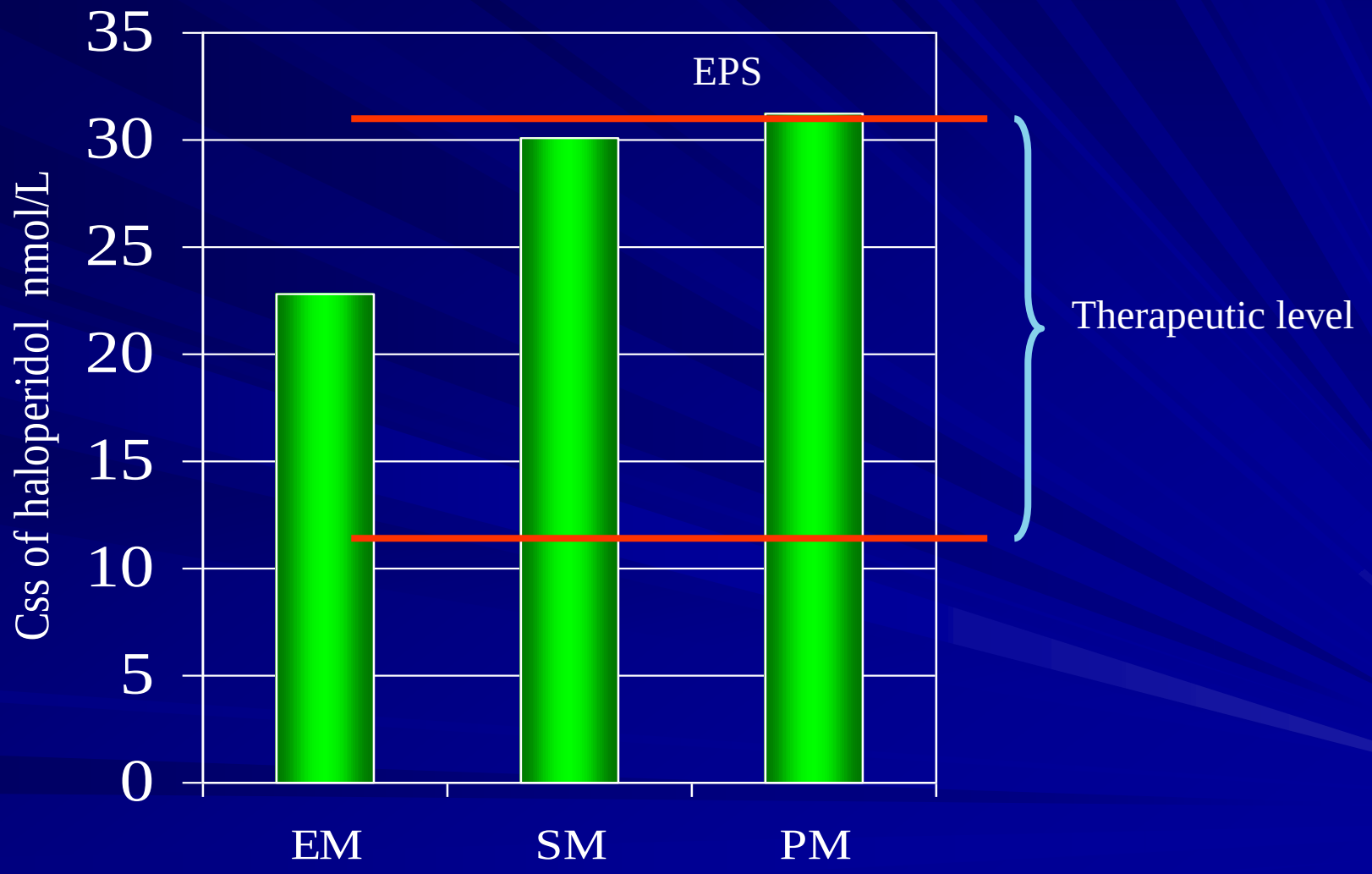
Antipsychotics: Collazo et al 1996



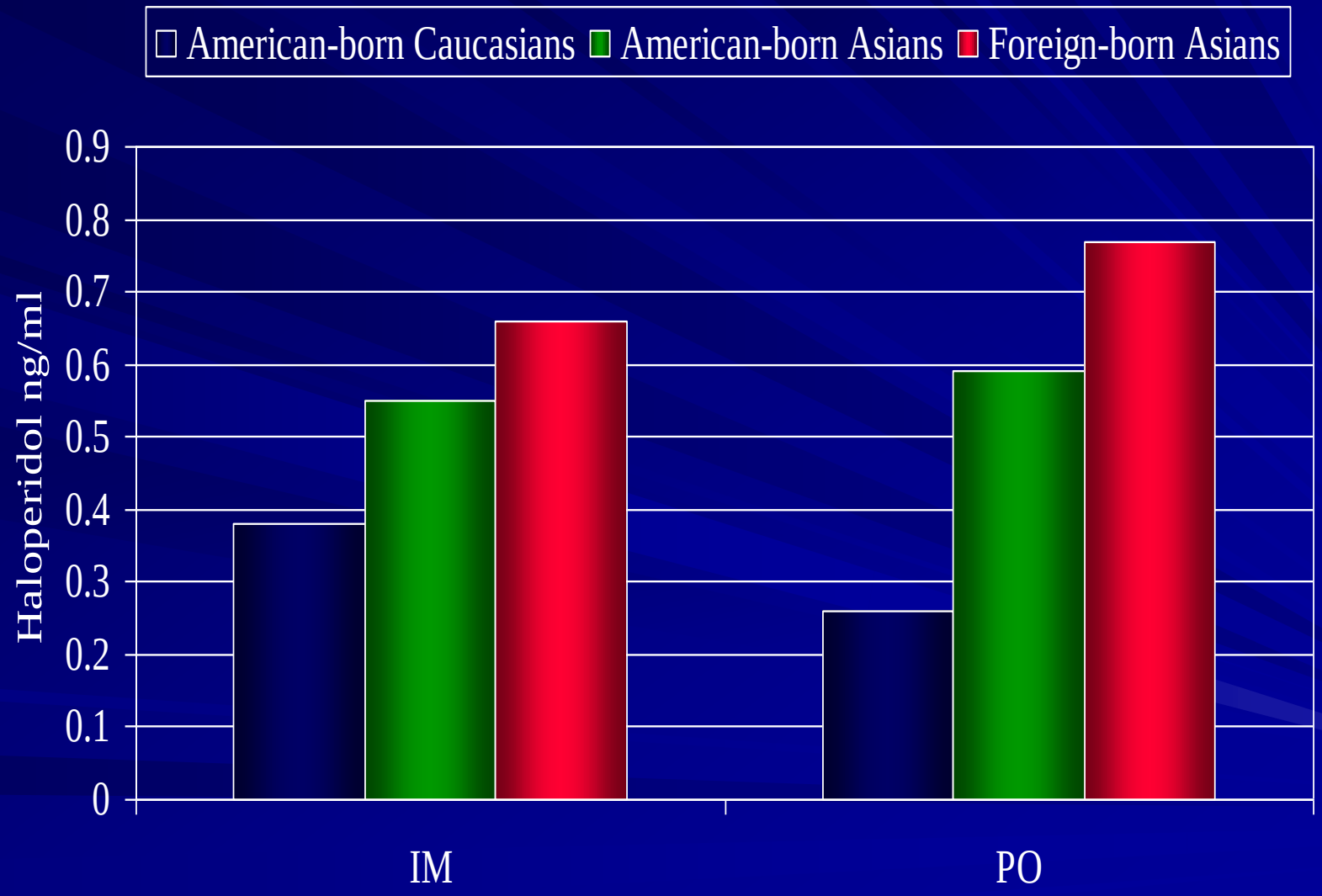


Asian Americans: Antipsychotics
Haloperidol and the CYP2D6*10 allele



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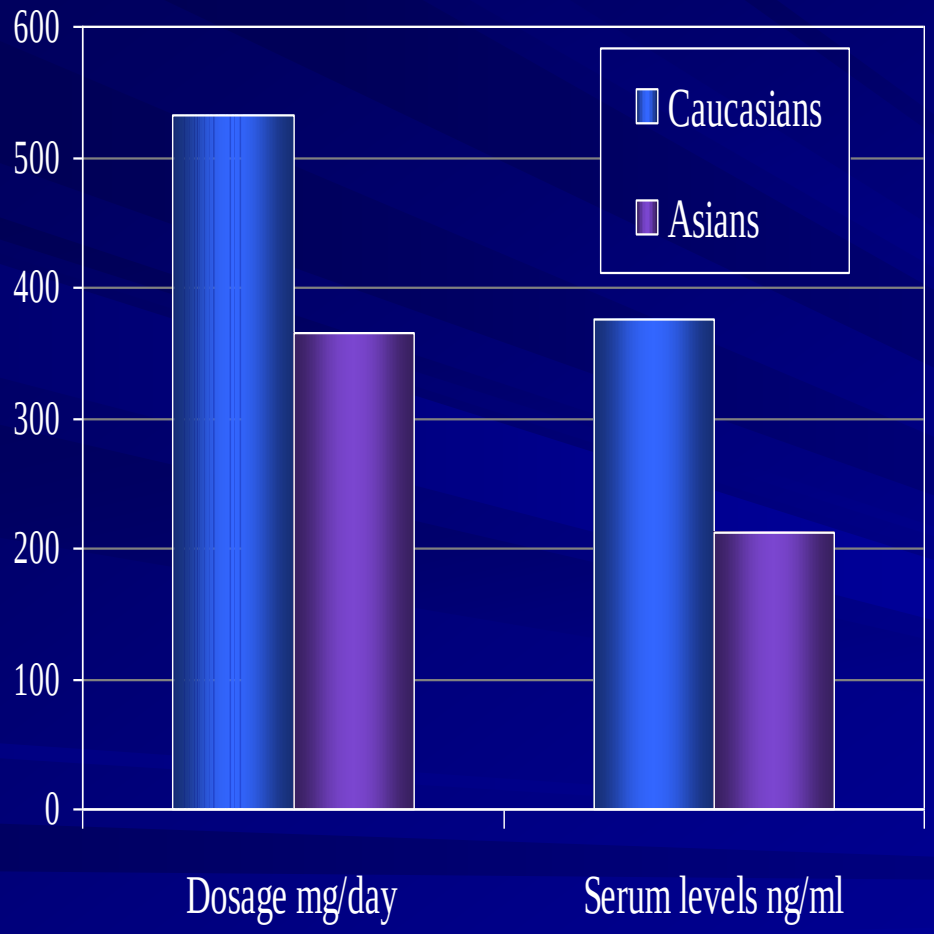
Asian Americans: Antipsychotics
Clozapine: Dosage, Serum Levels, & Response



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

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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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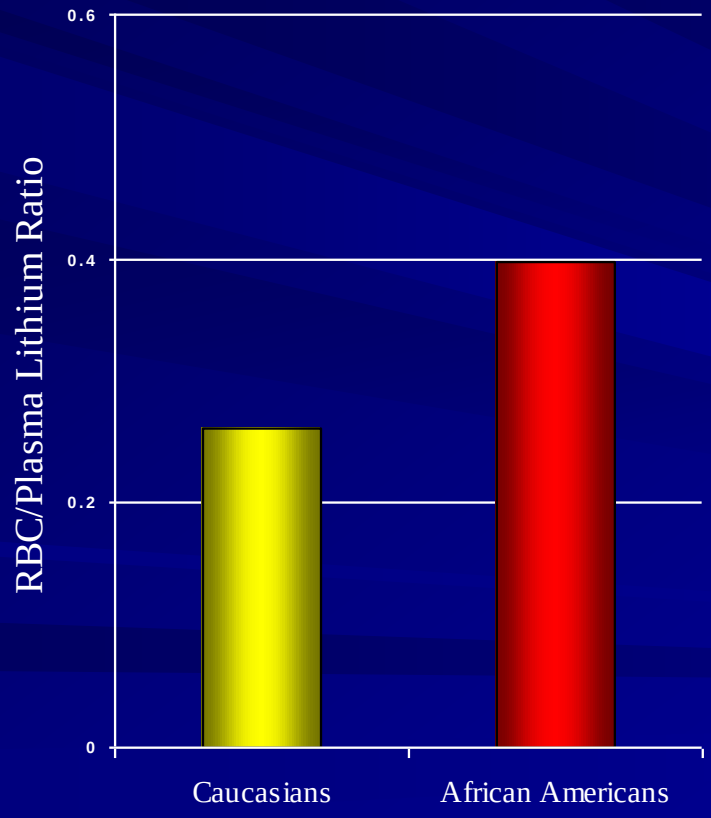
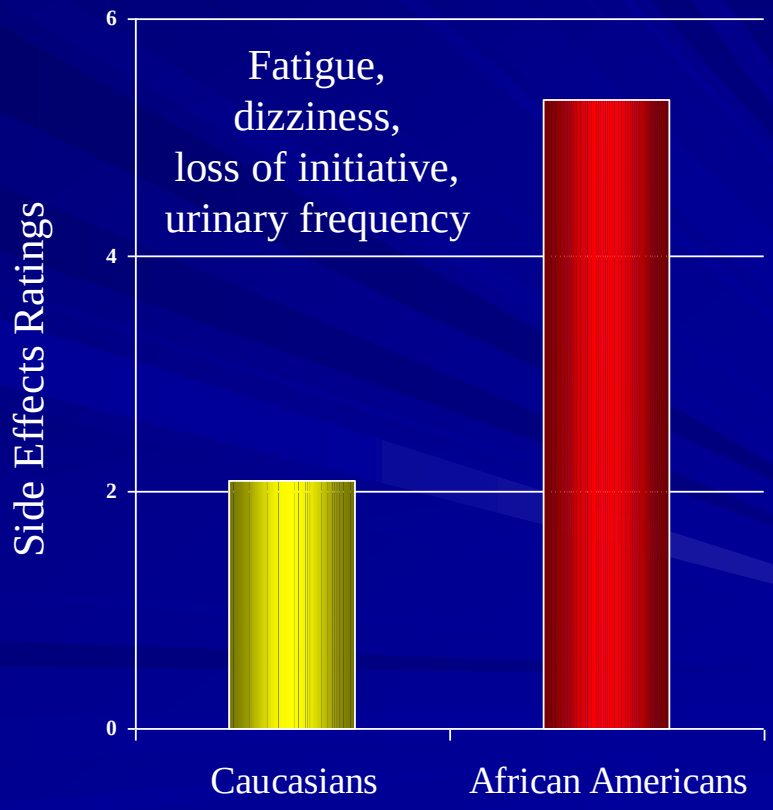
RBC Lithium counter transport associated with side effects in African Americans

RBC/Plasma Lithium Ratio: Ethnic Variation

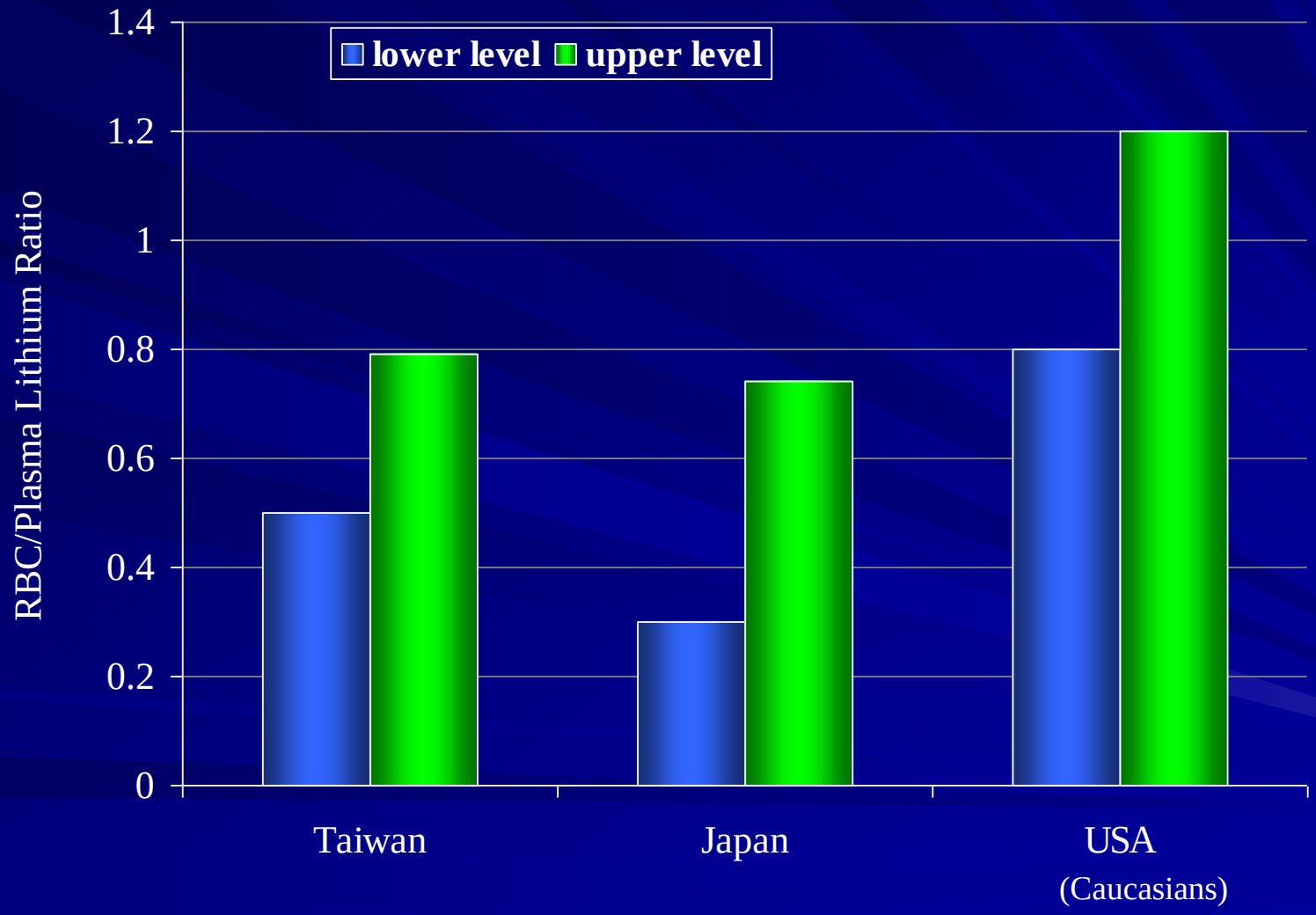


Lithium Side Effects Ratings: Ethnic Variation



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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Asian Americans
Carbamazepine induced skin hypersensitivity

- The rate of carbamazepine induced skin hypersensitivity among Asians is much higher compared to its Caucasian counterpart.
- There is a strong association in Han Chinese between a genetic marker, the human leukocyte antigen HLA-B*1502, and Stevens-Johnson syndrome induced by carbamazepine.
- HLA-B*1502 does not seem to be a marker for all forms of CBZ-induced hypersensitivity in a Caucasian population.
- In 2007, U.S. FDA recommended a genetic test for HLA B1502 for screen prior initiating carbamazepine treatment for people with Asian origin.

Chung et al, 2004; Chen et al, 2011; Alfirevic et al, 2006; Lim et al 2008

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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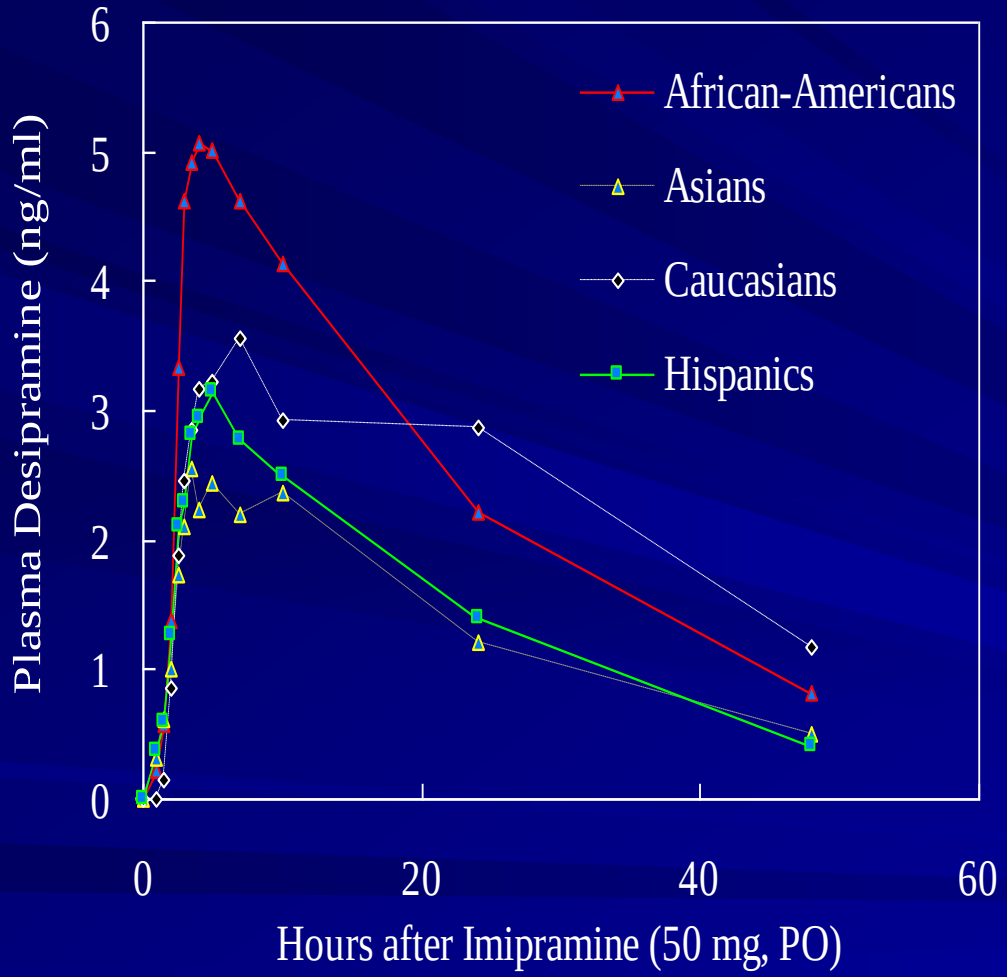
Ethnic Variation in Imipramine Metabolism



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
- The treatment outcomes of Spanish-speaking Hispanic are different from that of English-speaking counter part in STAR*D trial.

Mezzich & Raab, 1980; Marcos & Cancro, 1982; Escobar & Tuason, 1980; Gaviria et al, 1986; Lesser et al, 2008

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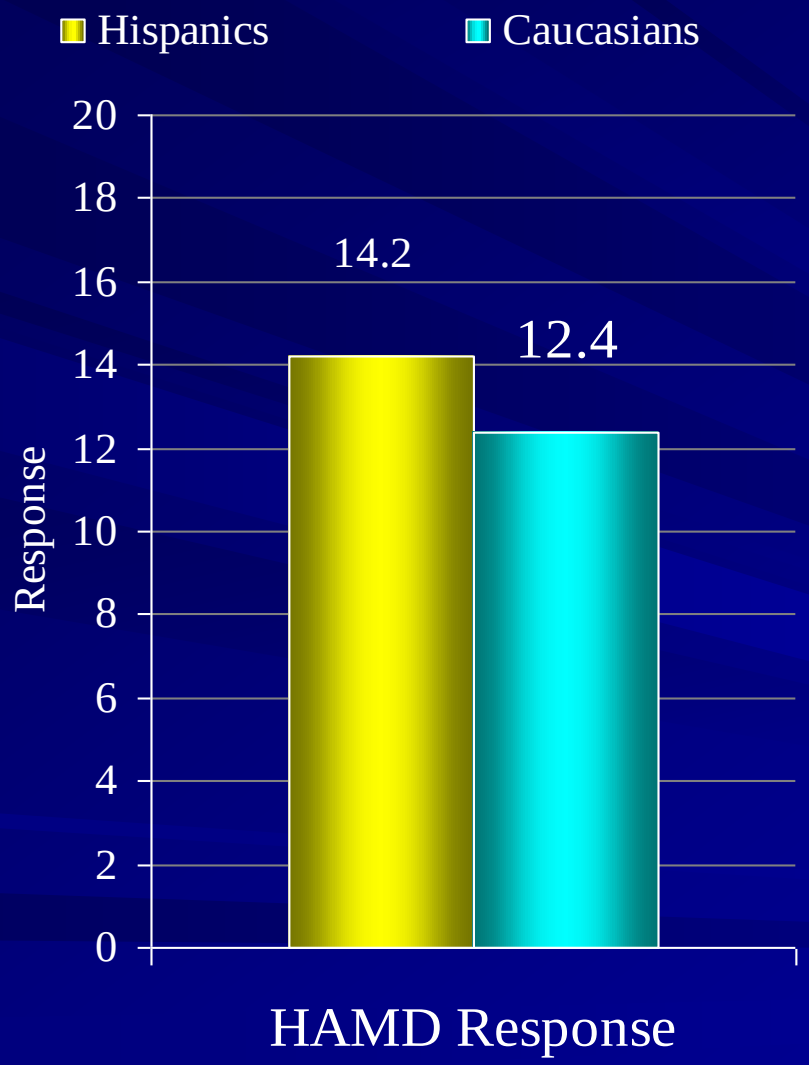
Hispanics: Antidepressants
Marcos and Cancro 1982

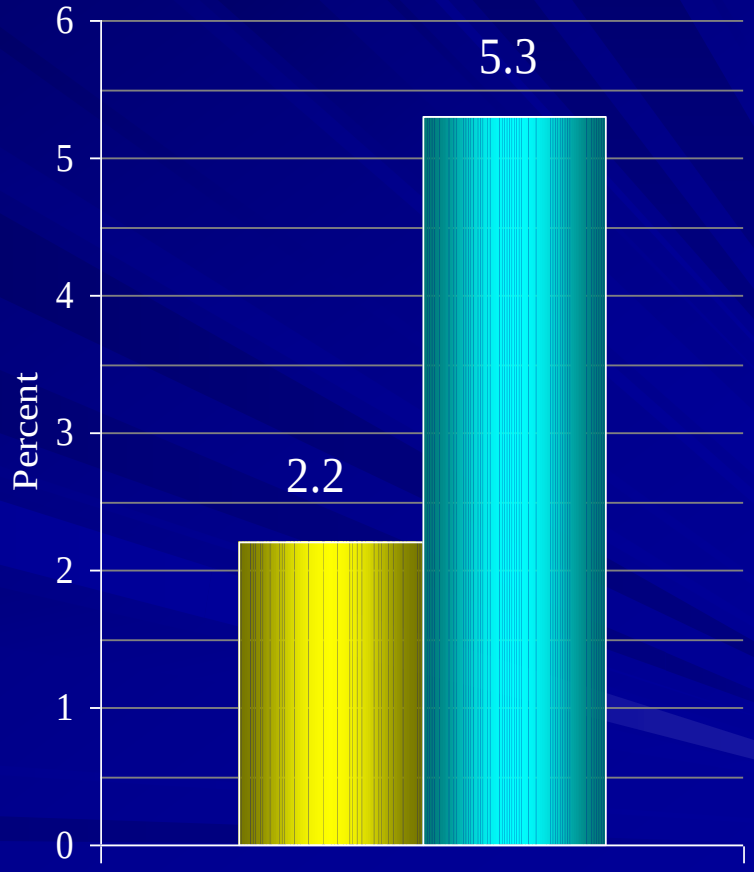
41 Hispanic (PR) and 21 Caucasian female outpatients

- 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

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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

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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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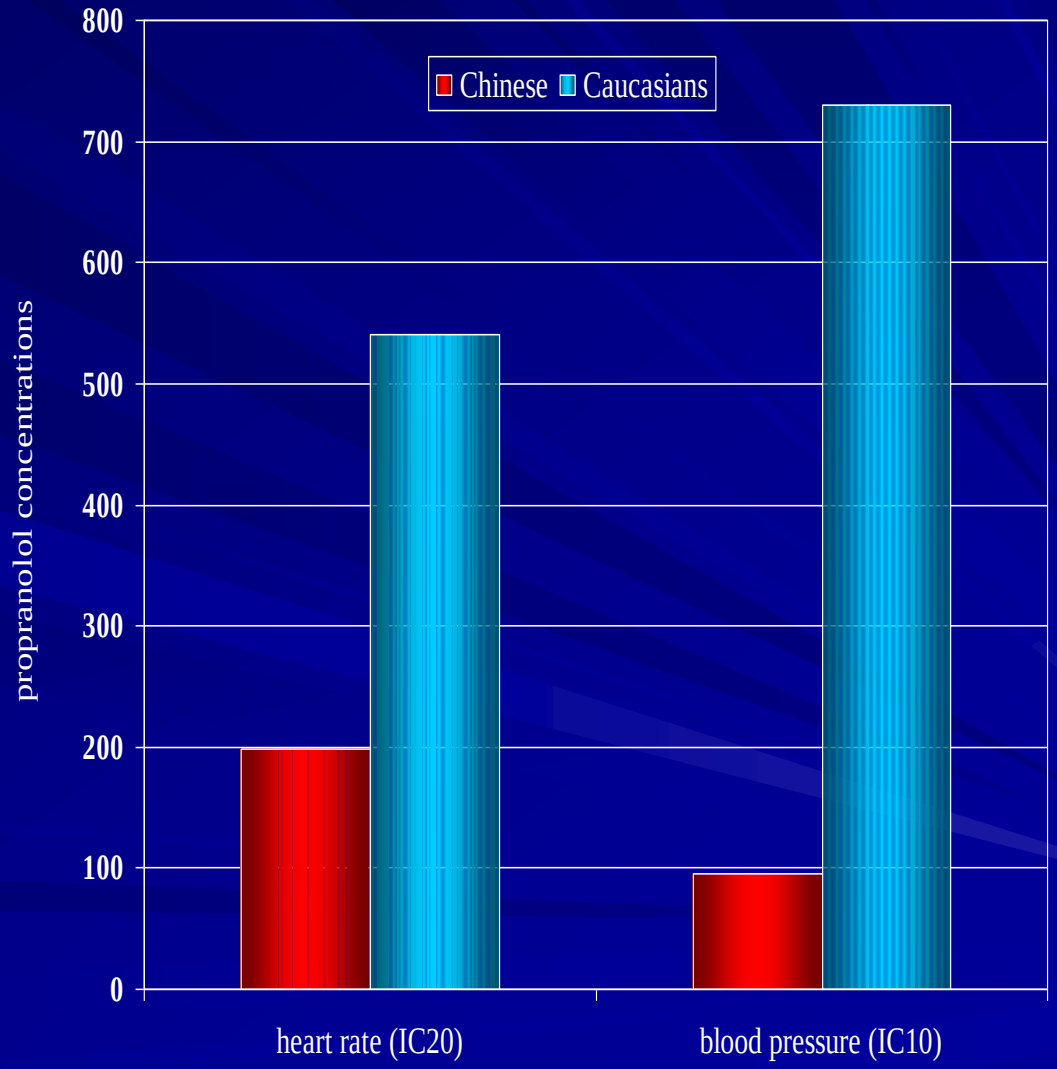
Propranalol Response: Chinese vs. Caucasians

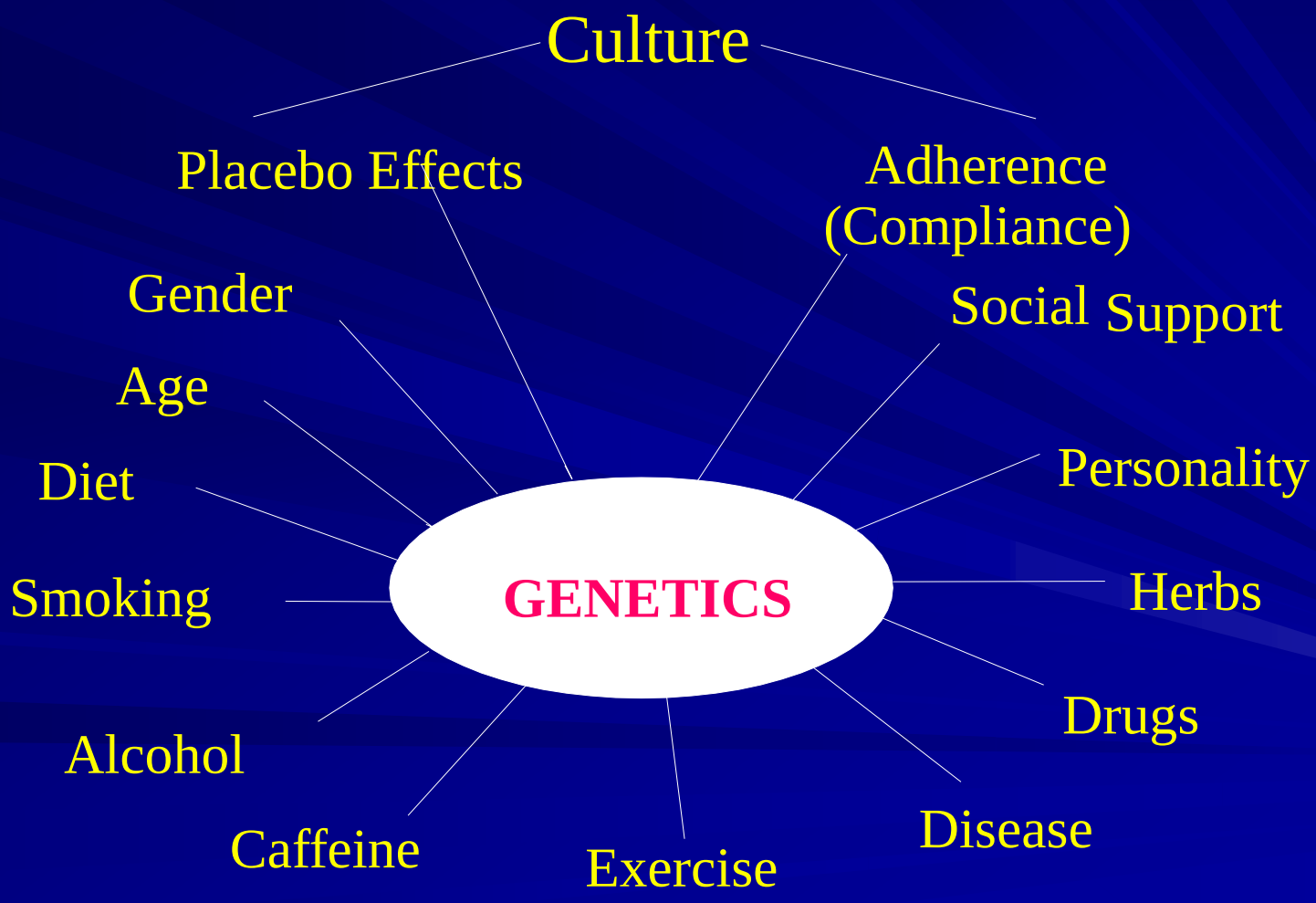
b-blocker propranalol

•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

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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

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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

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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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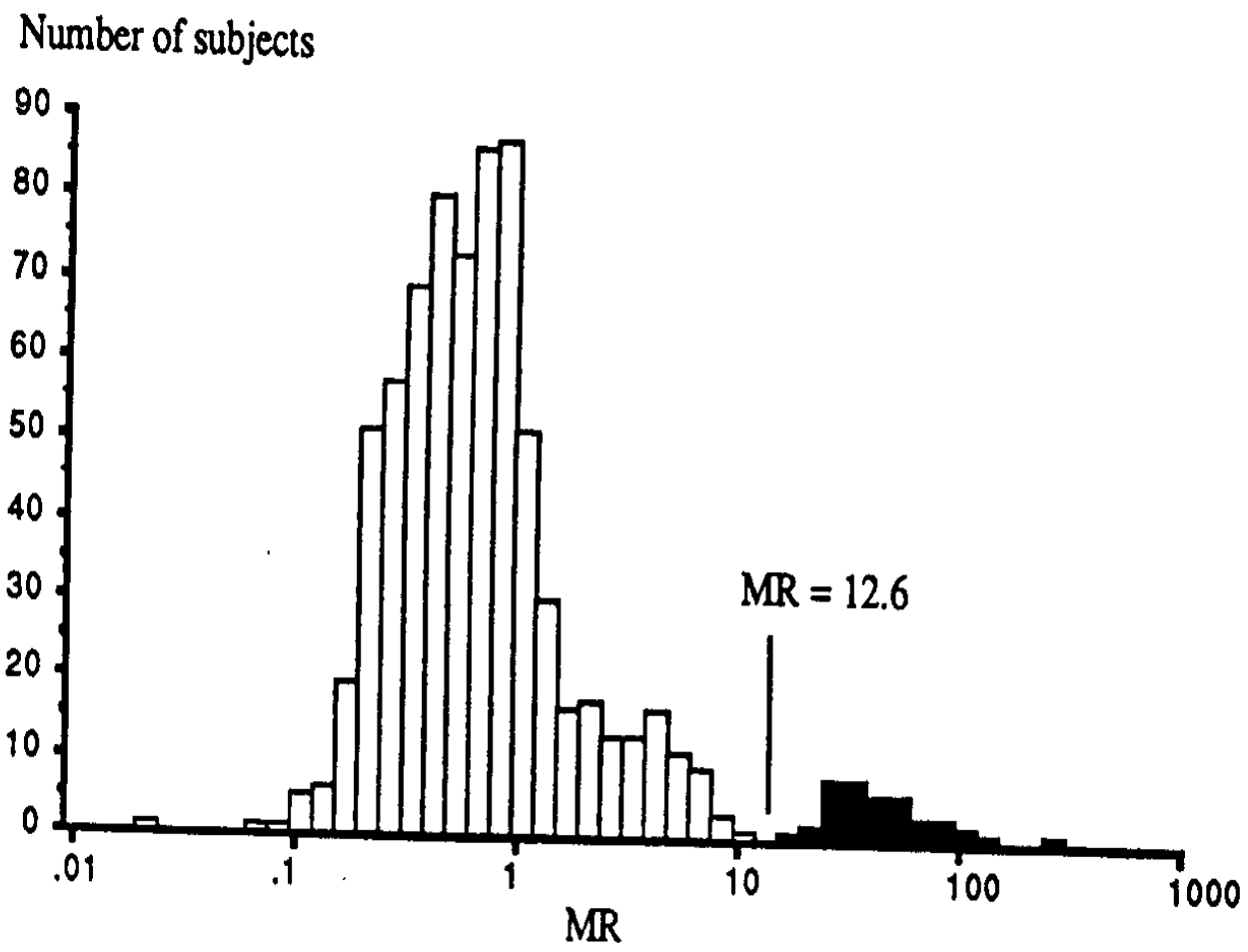
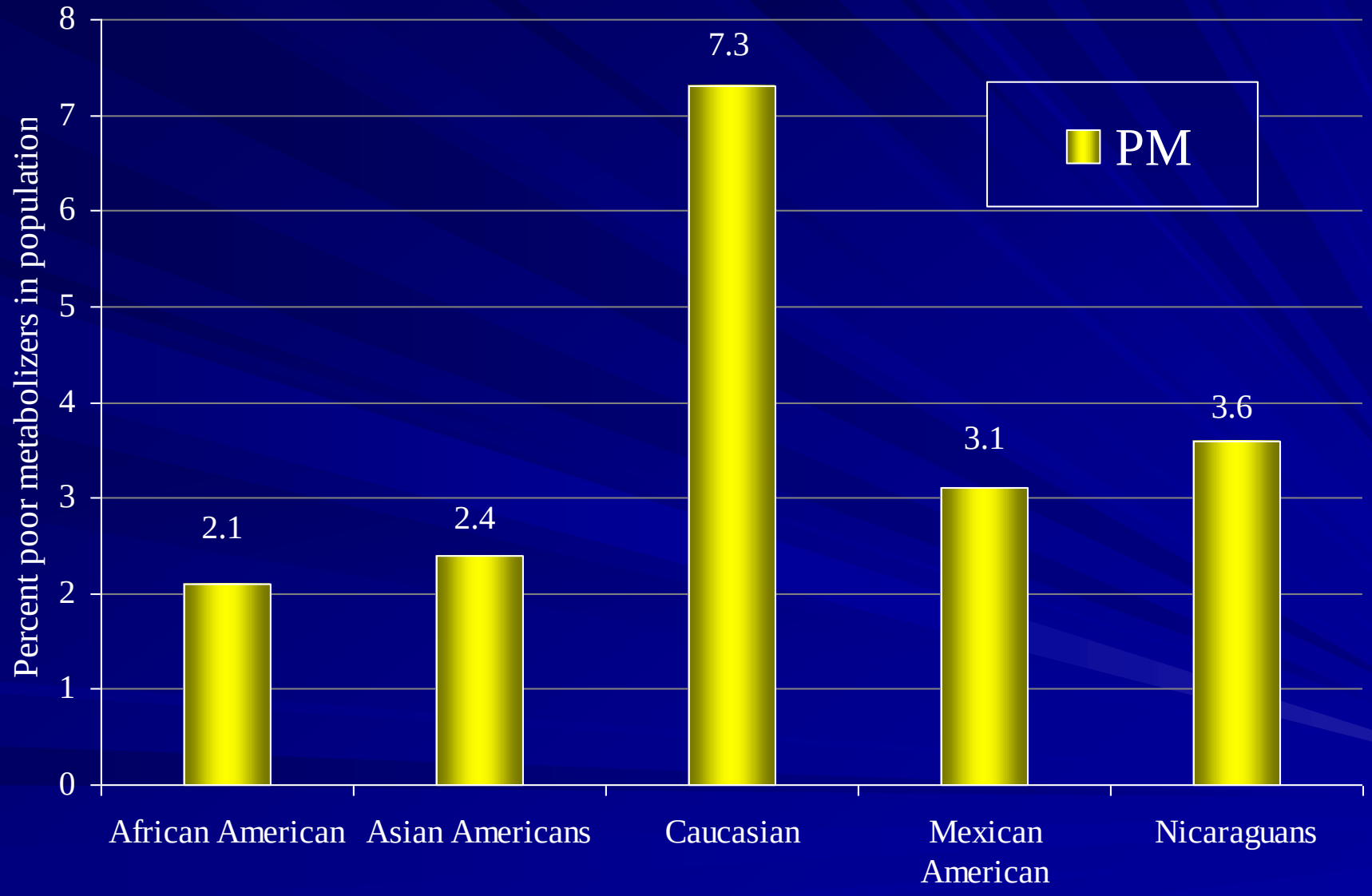
Distribution of CYP2D6 Activity in Caucasian Populations



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

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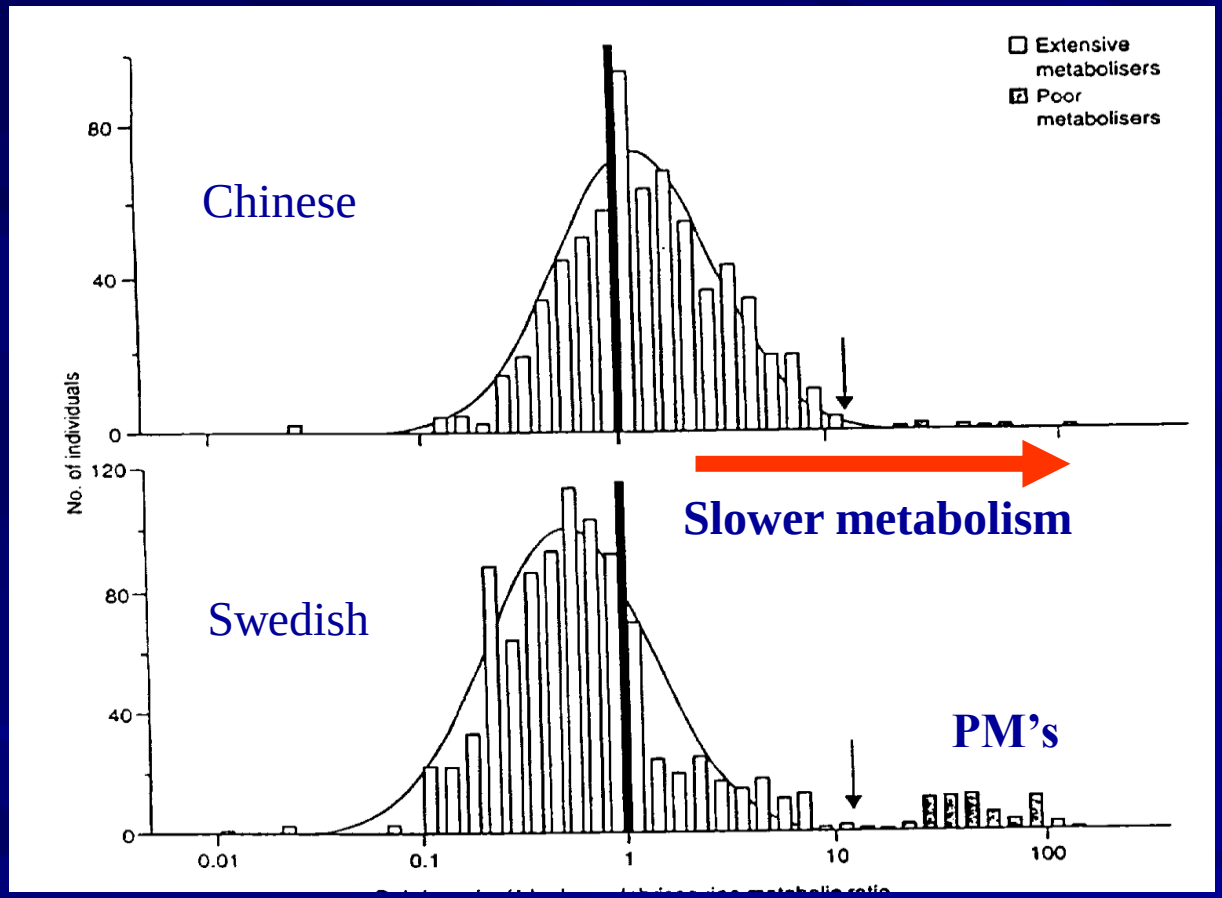
Ethnic Variation in CYP2D6 Activity



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

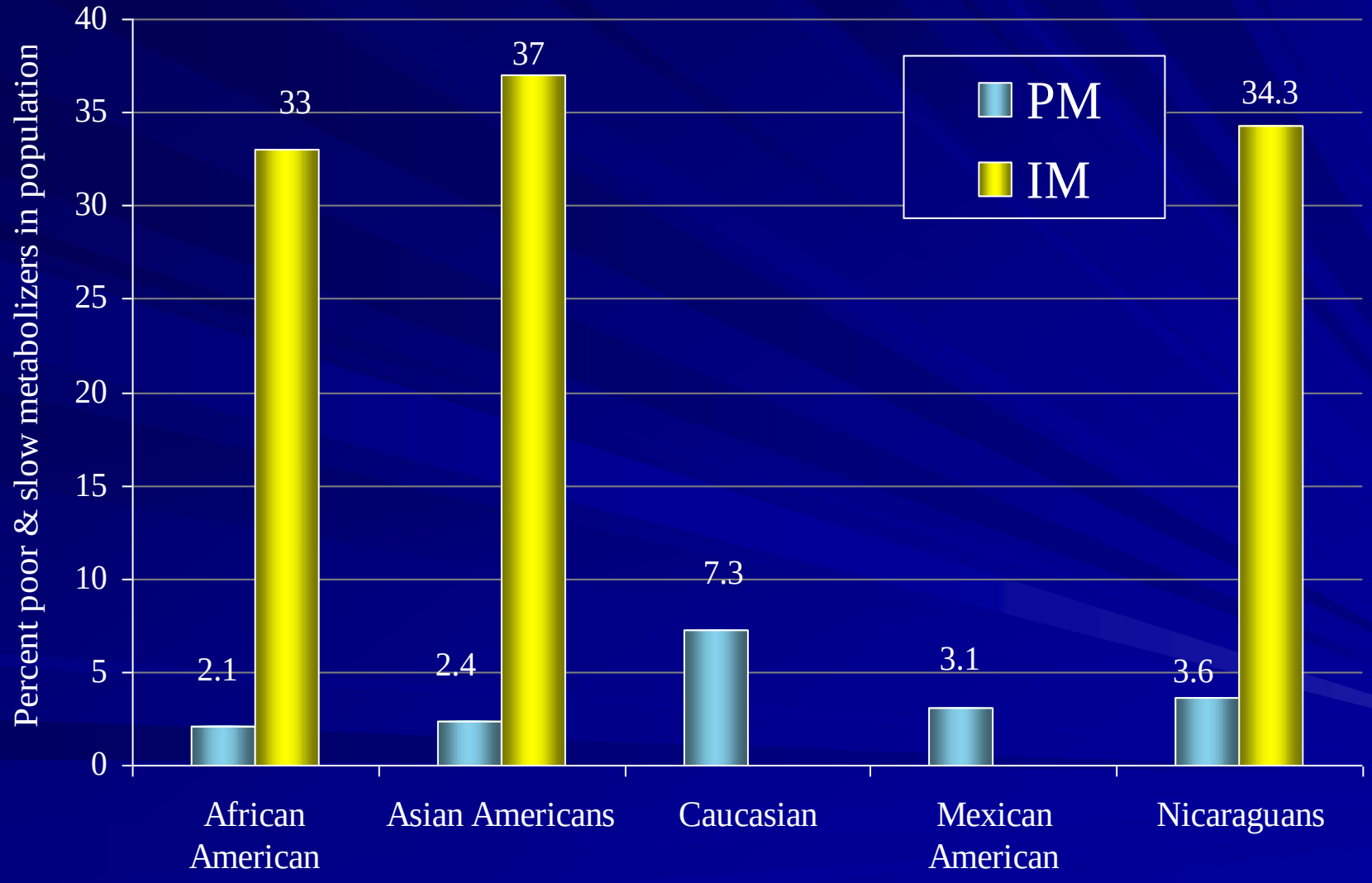
CYP2D6 Metabolic Rates

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

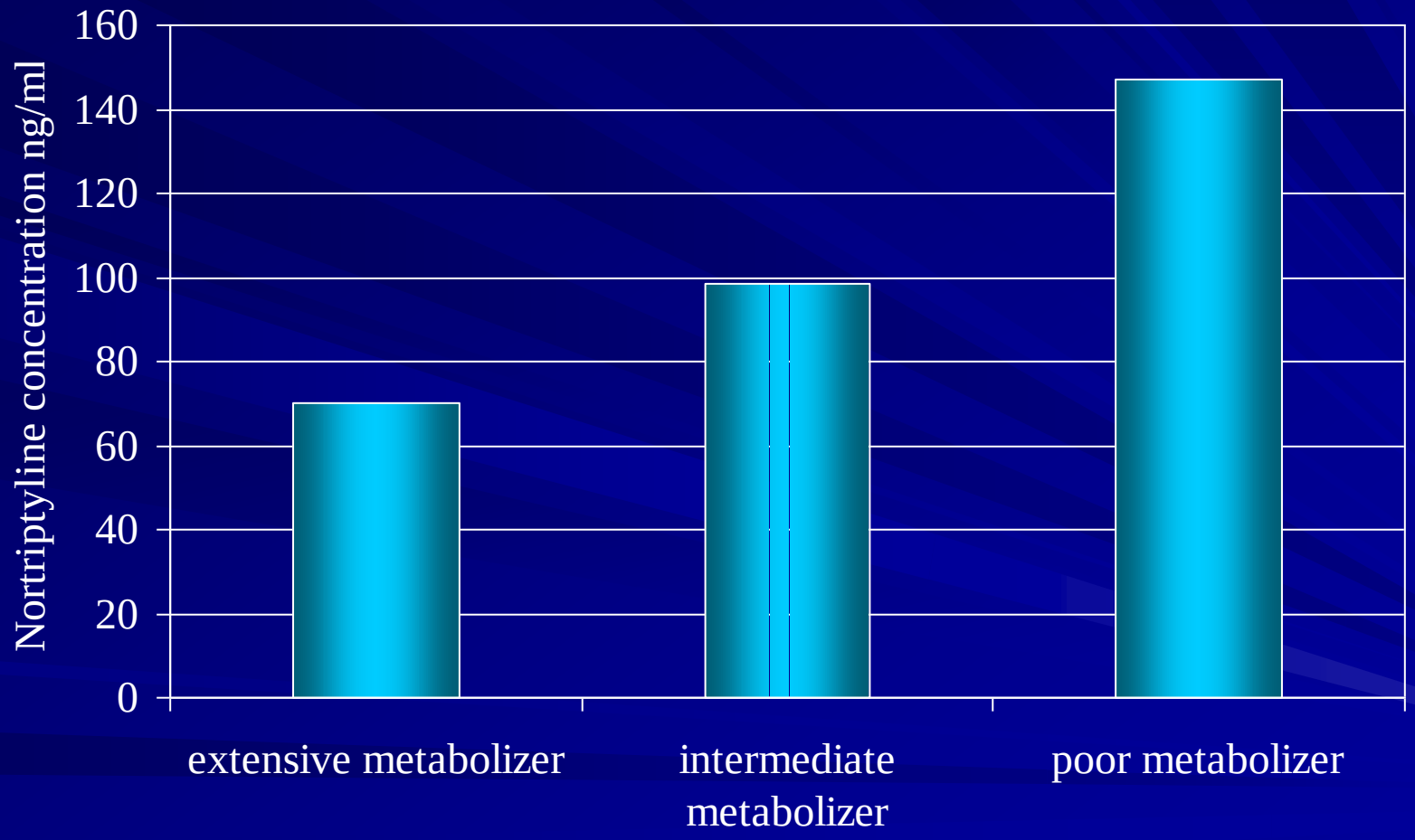
*

CYP2D6 Poor & Intermediate Metabolizers



adapted from Smith 2005

Impact of CYP2D6 Phenotype on Nortriptyline Plasma Levels in Japanese:



Morita, et al, 2000

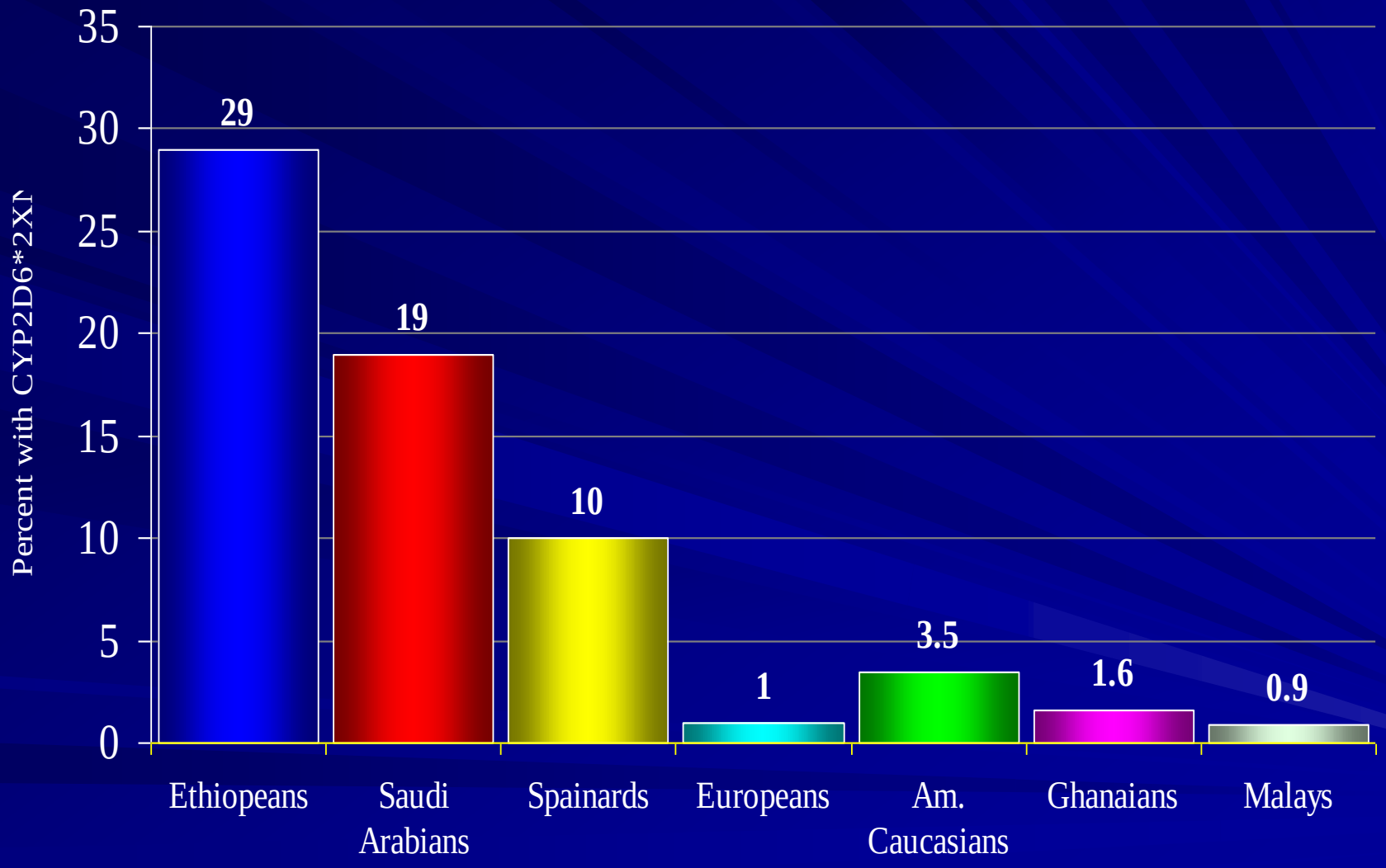
CYP2D6 Inhibitors

- 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.

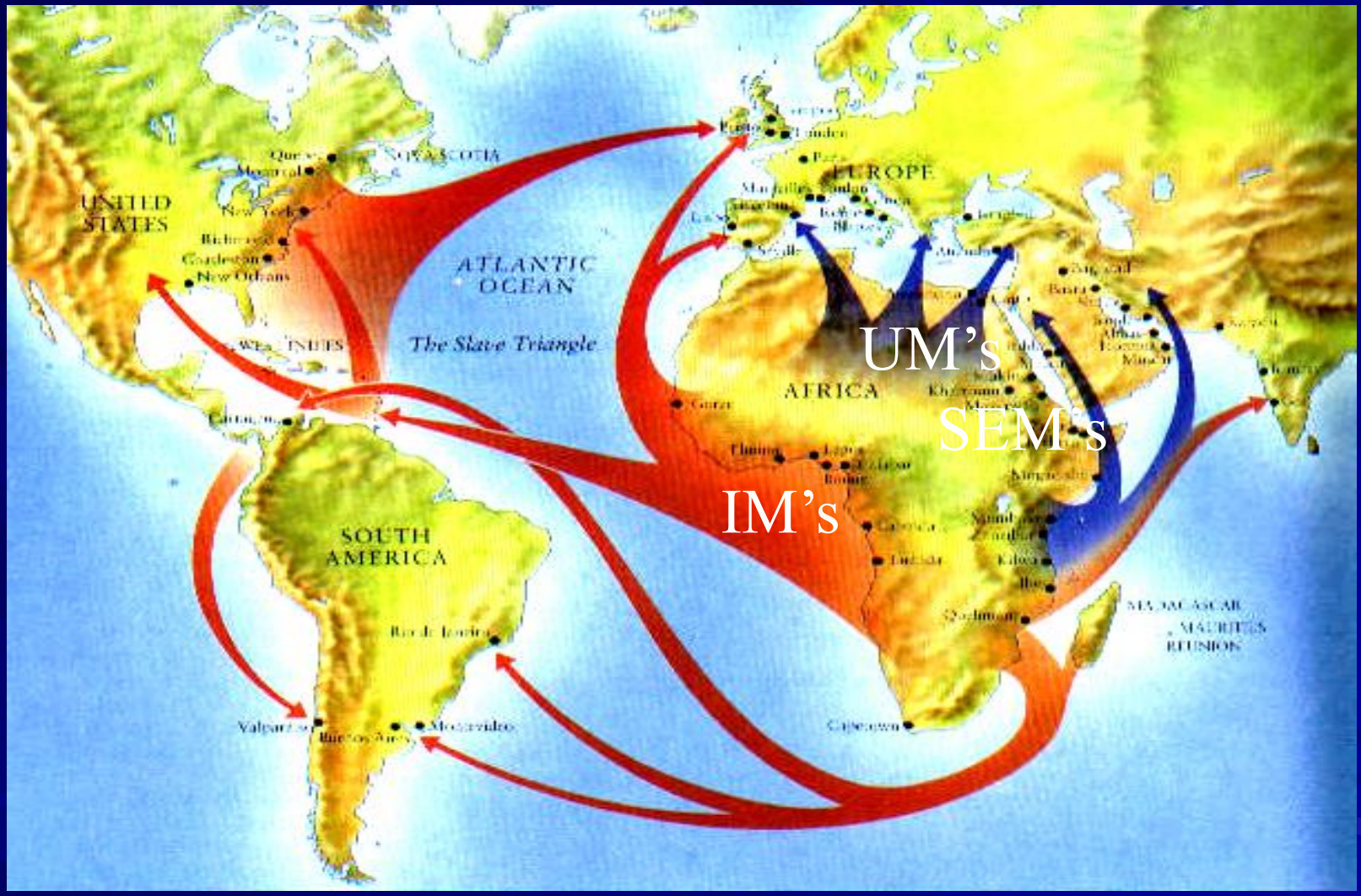
*

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

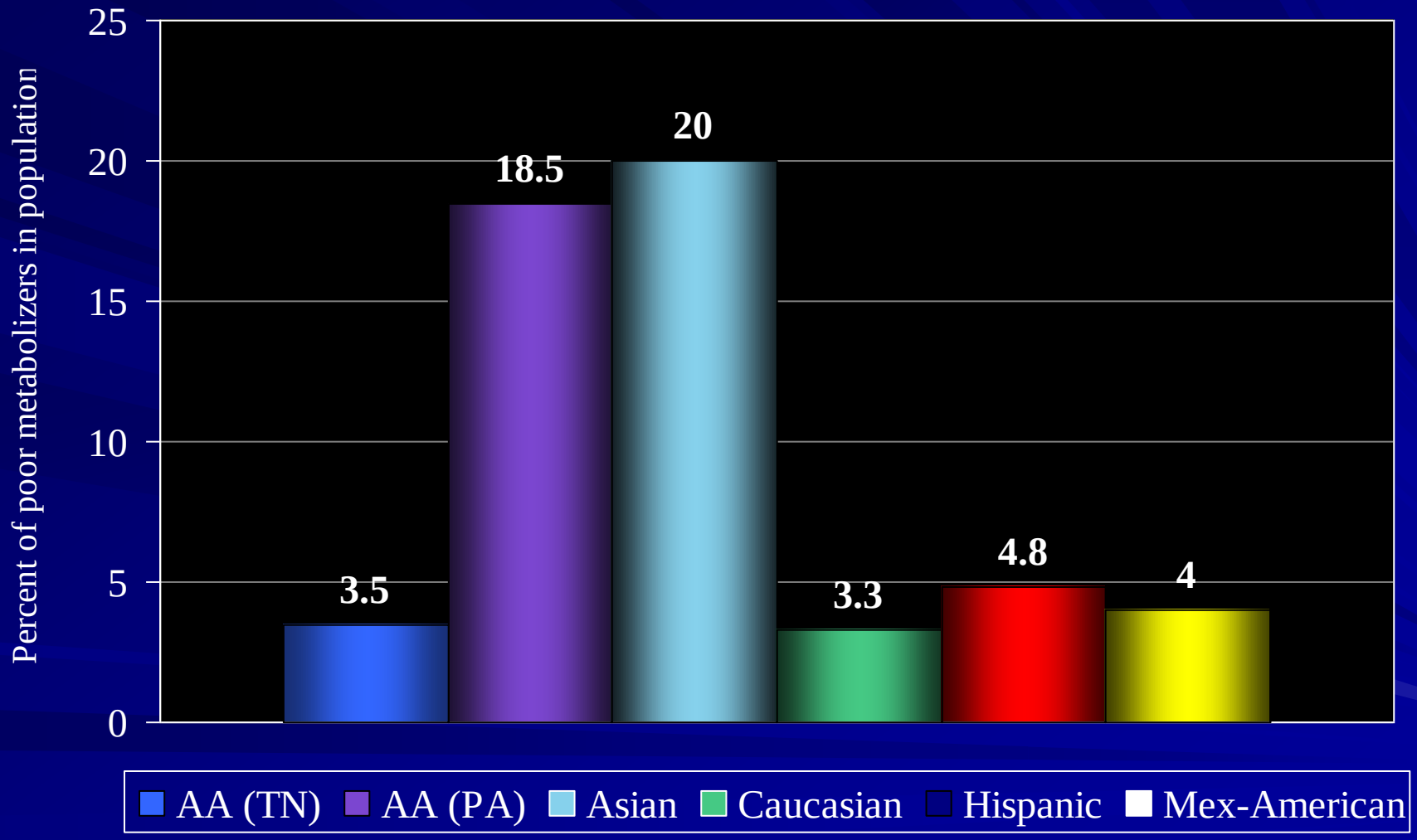
- propranolol, hexobarbital, mephobarbital
- proguanil, omeprazole, S-mephenytoin

*partial route of metabolism

adapted from Smith 2005

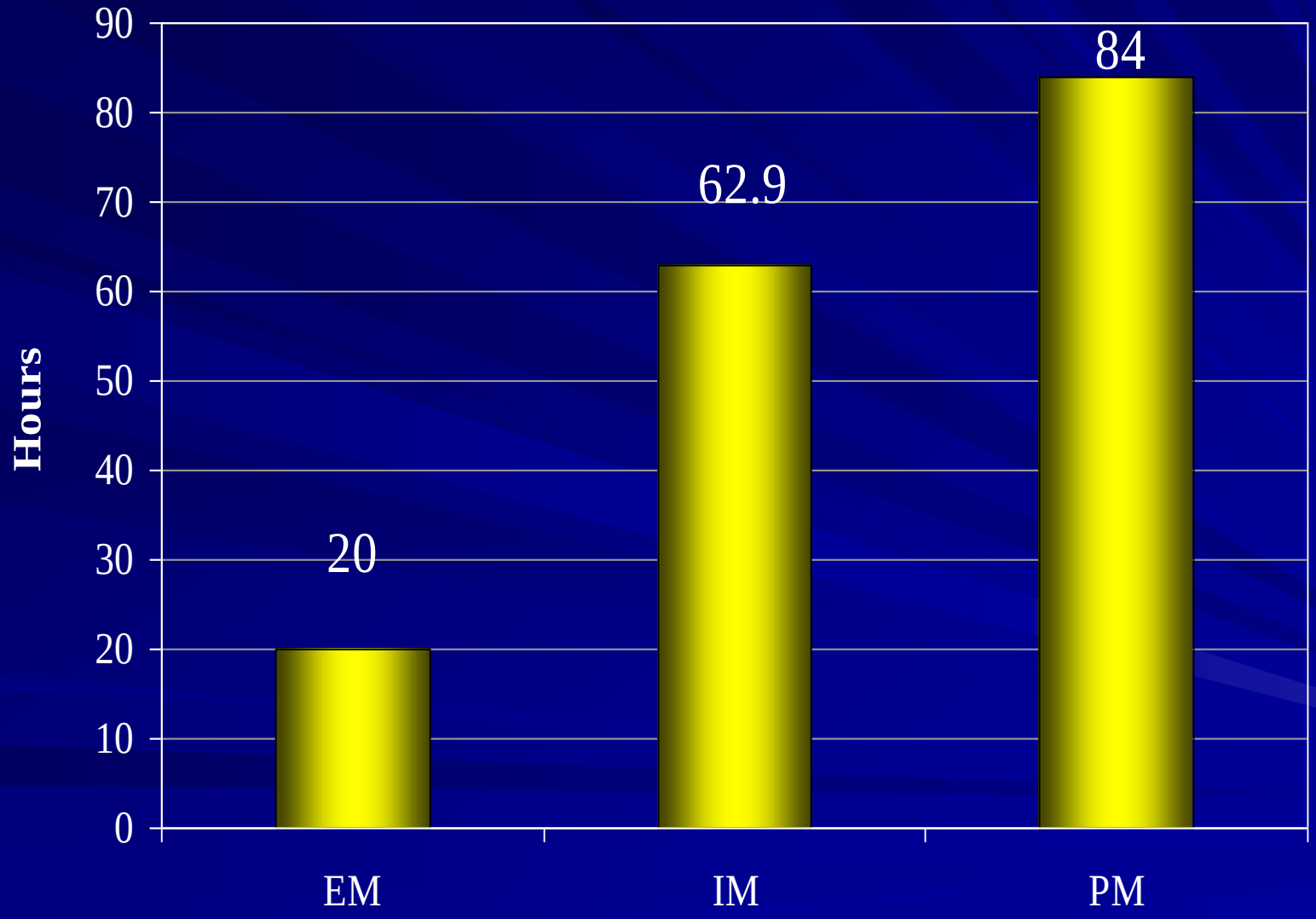
*

Poor Metabolizers (PM) of CYP2C19



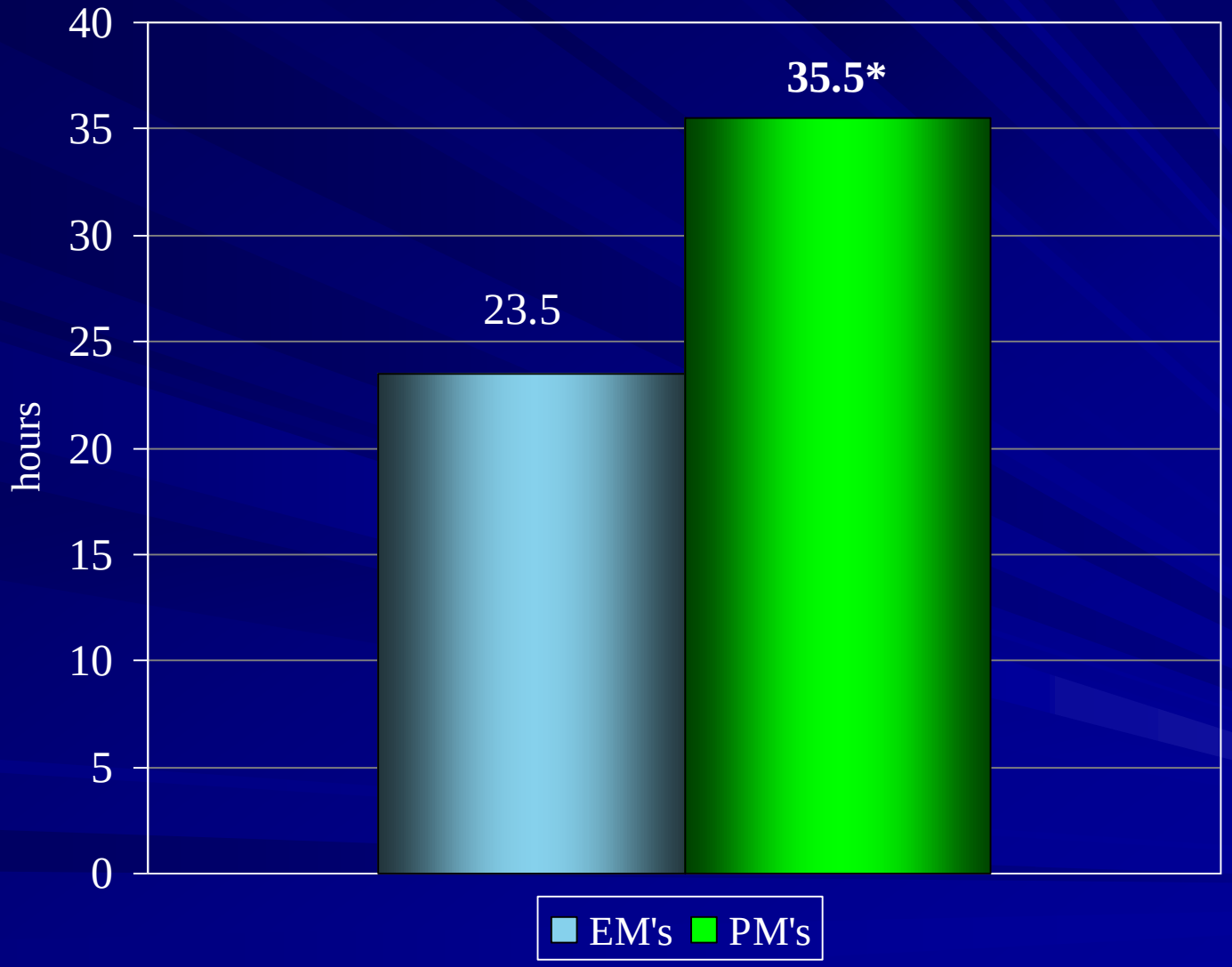
adapted from Smith 2005

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

*

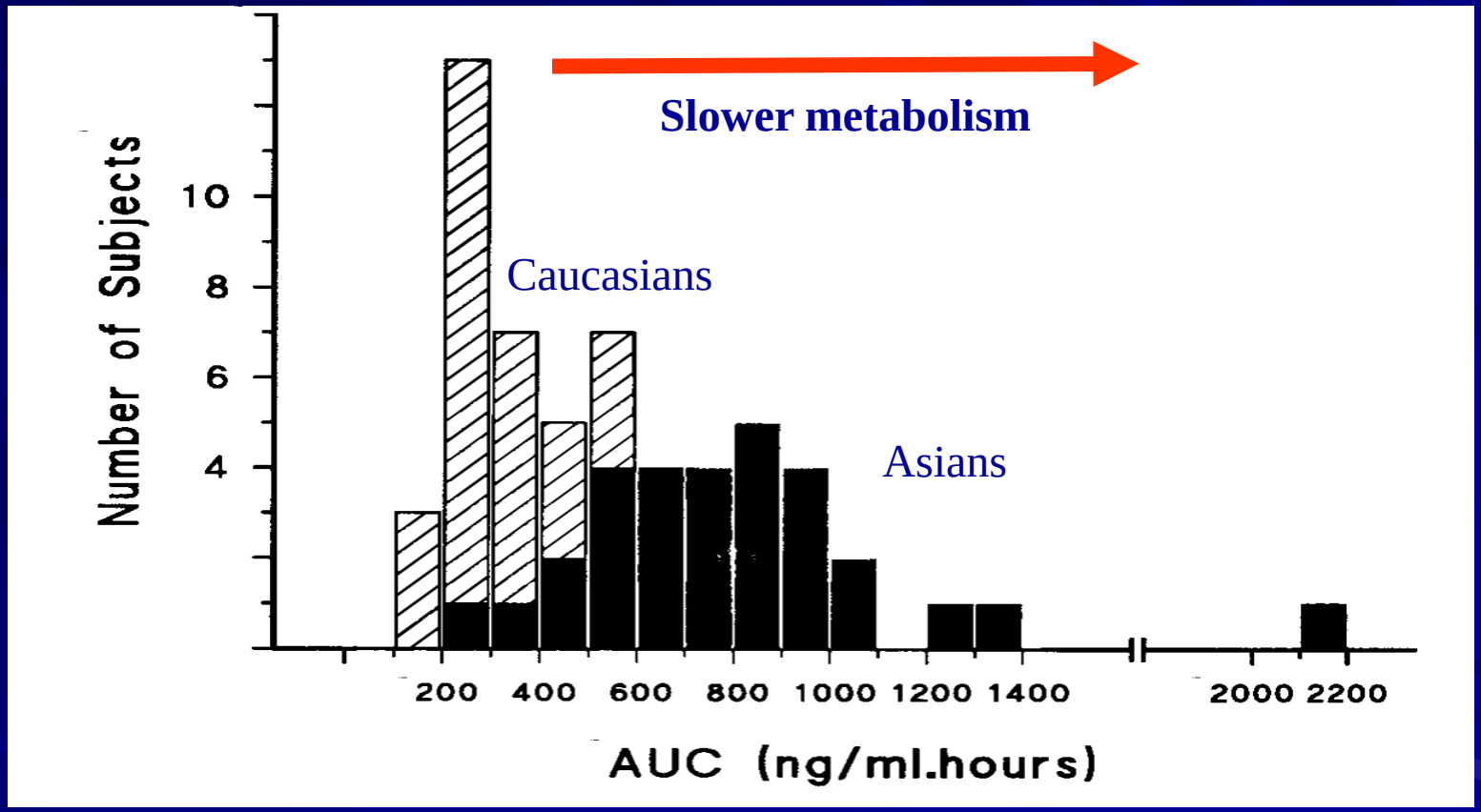
CYP3A4
(Nifedipine oxidase)

- 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

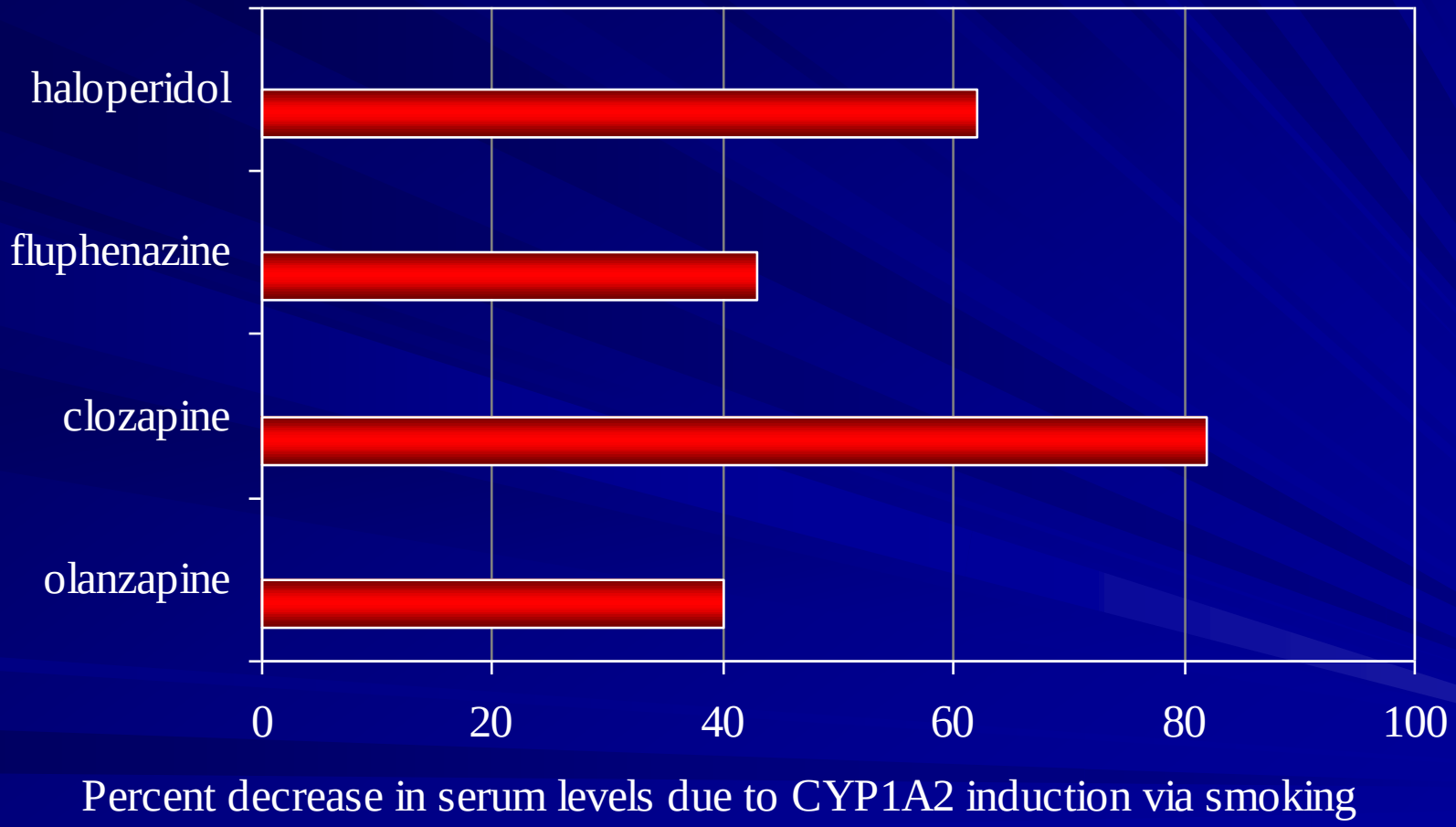
Mendoza et al 1991; Agarwal, et al 1990

Interactions of Food Ingredients with CYP450 Enzymes, for example, 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

Impact of Tobacco Smoking on Plasma levels of Antipsychotic Medications



Bozikas et al, 2004

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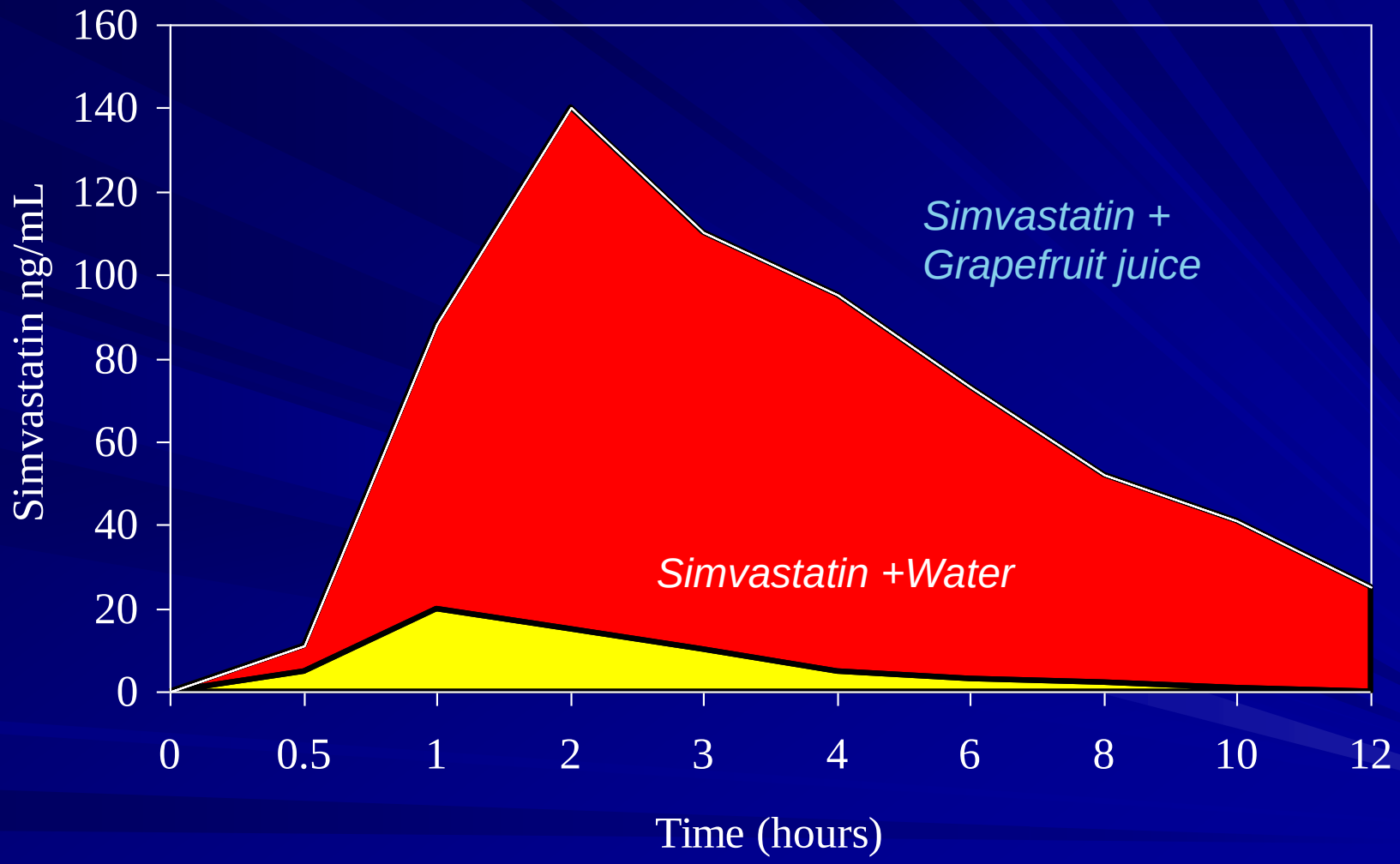
Simvastatin/Grapefruit Juice



Lilja et al, 1998

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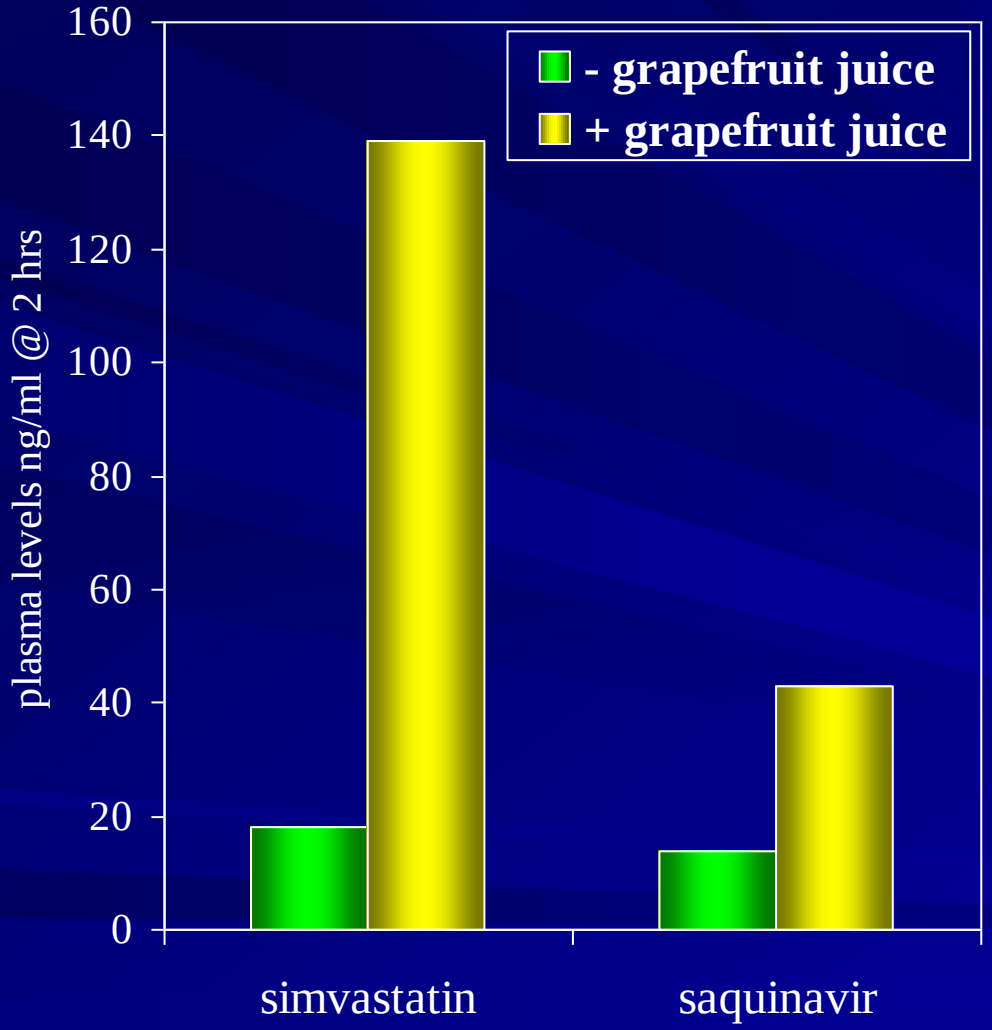
Grapefruit Juice Inhibits the Metabolism of Simvastatin and Saquinavir



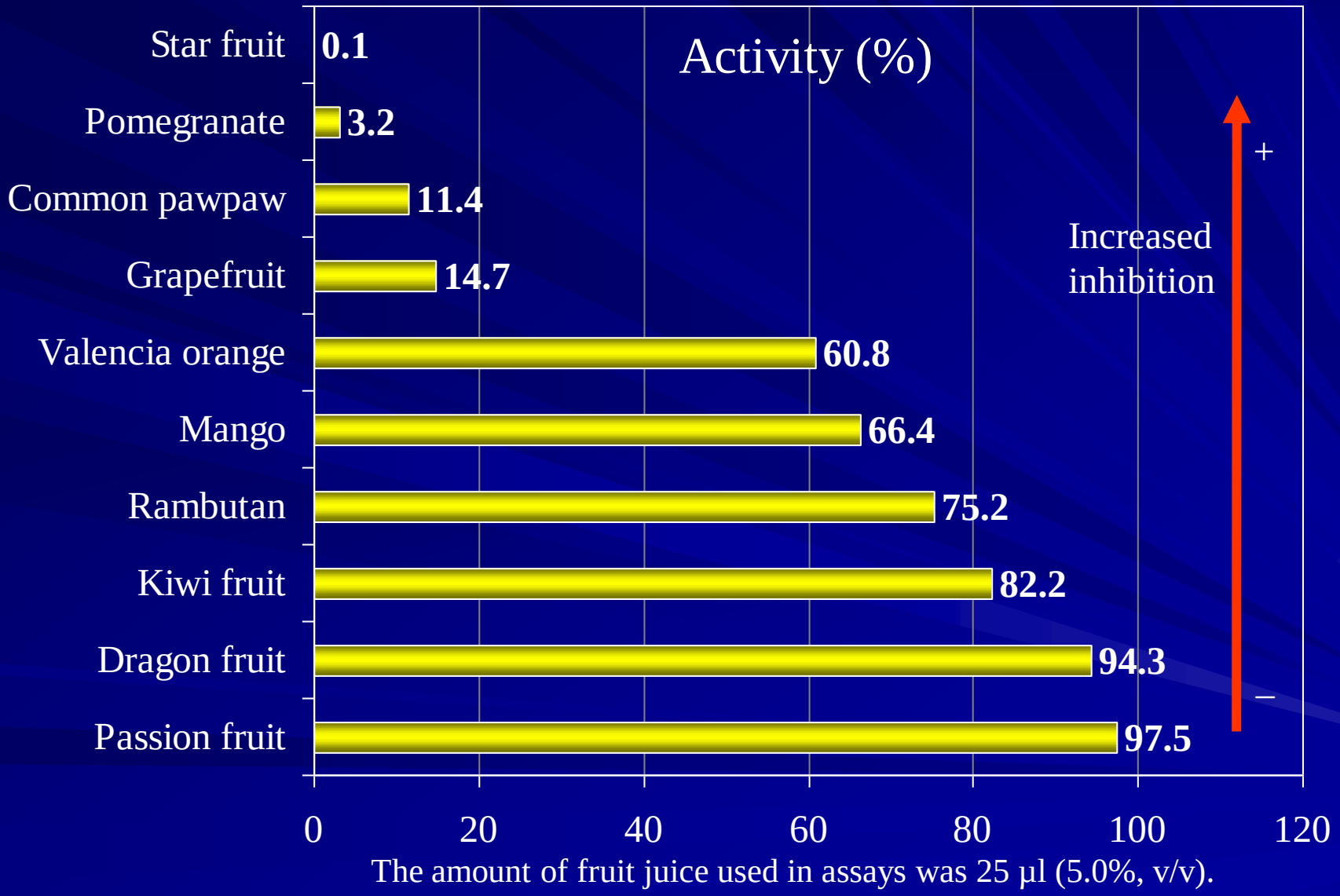
Grapefruit juice is a strong inhibitor of CYP3A4.
It inhibits the enzyme in the small intestine which allows more drug to be absorbed into the bloodstream.

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

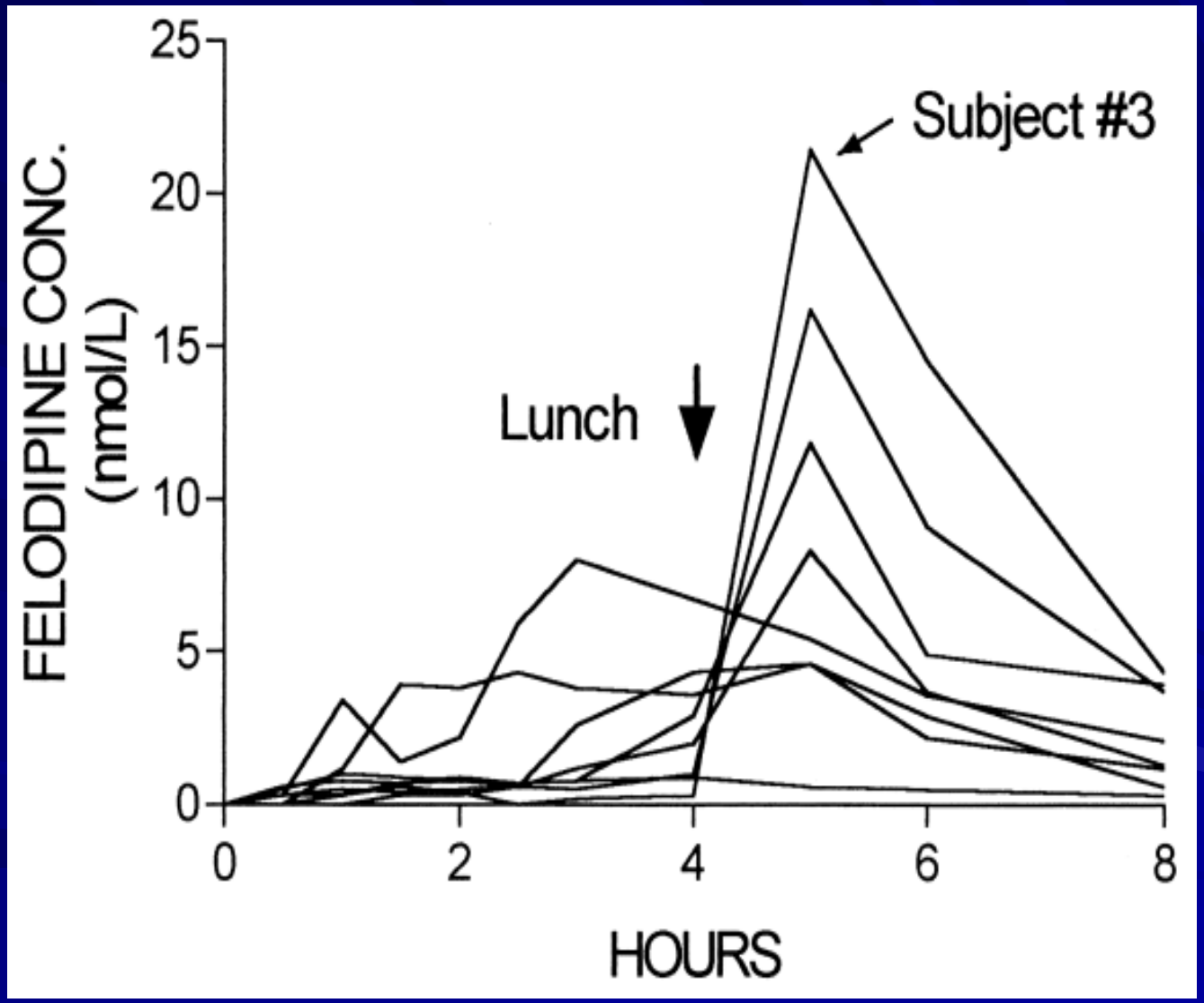
*

Effects of Tropical Fruit Juice on *in vitro* CYP3A4 Activity



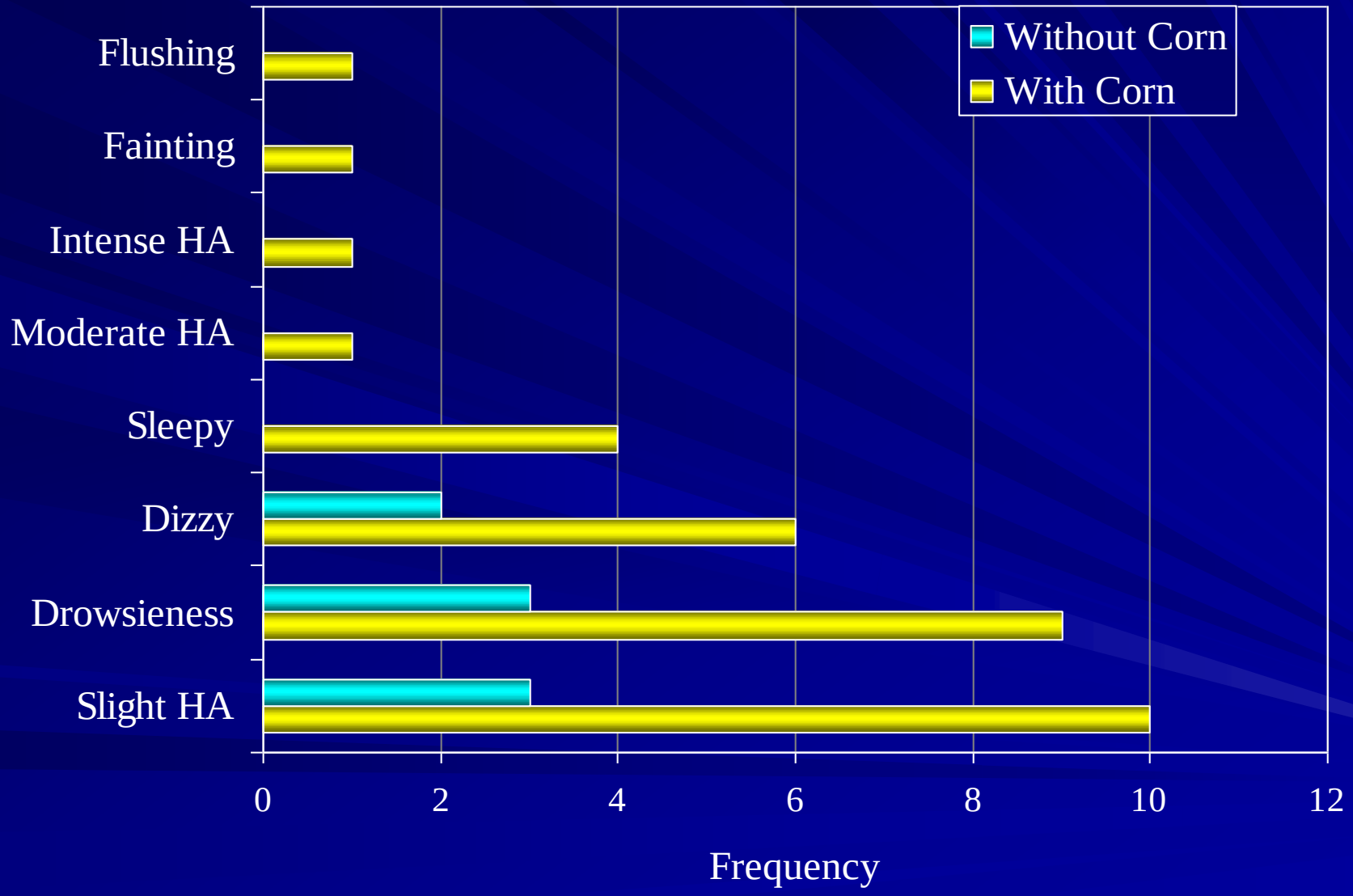
Hidaka et al, Drug Metab Dispos. 2004

Felodipine & Cabernet Sauvignon



Bailey et al, 2003

Nifedipine Side Effects and Dietary Corn Ingestion



Palma-Aguire, 1999

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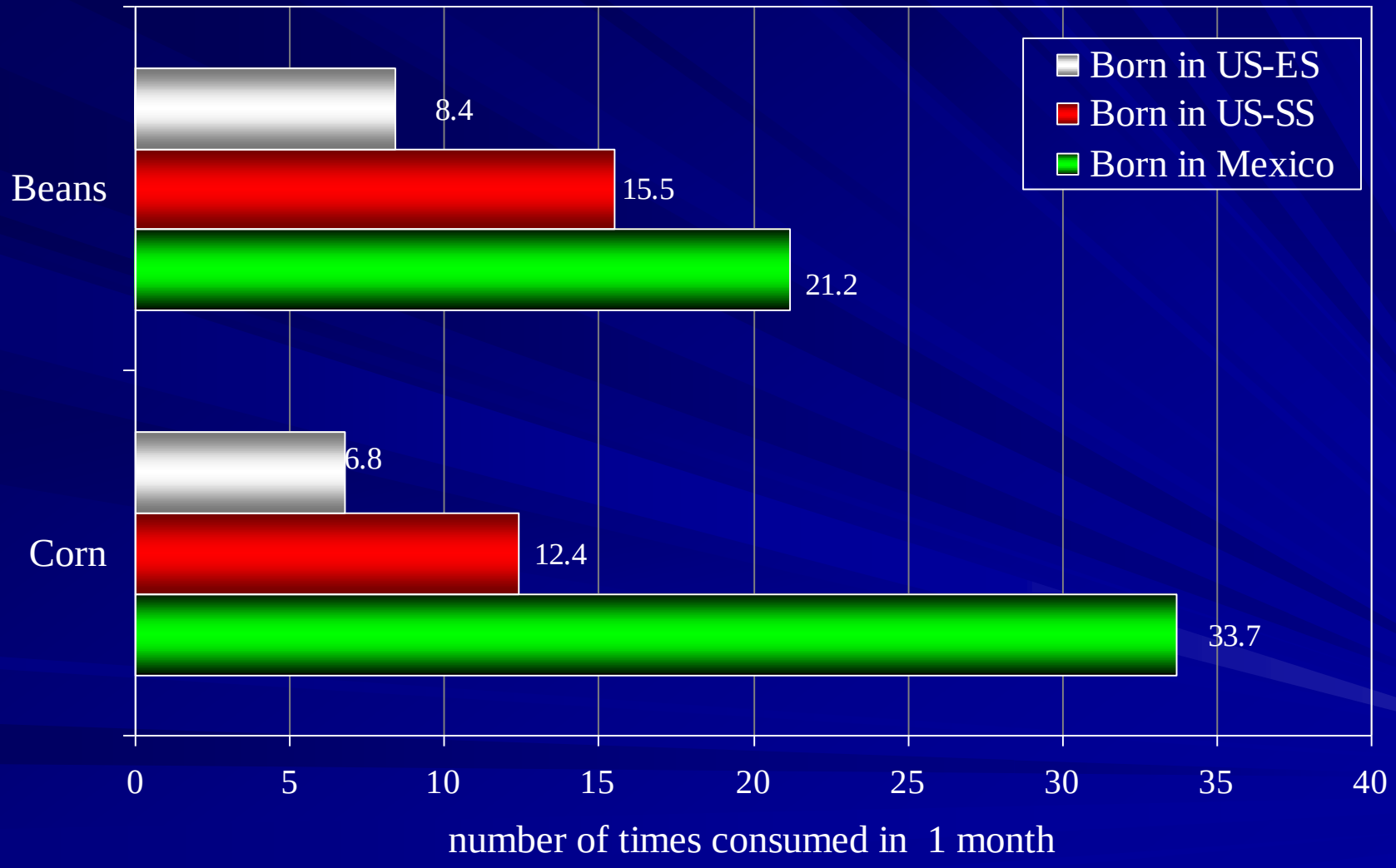
Diet Variation, Migration & Acculturation Among Mexican American Women



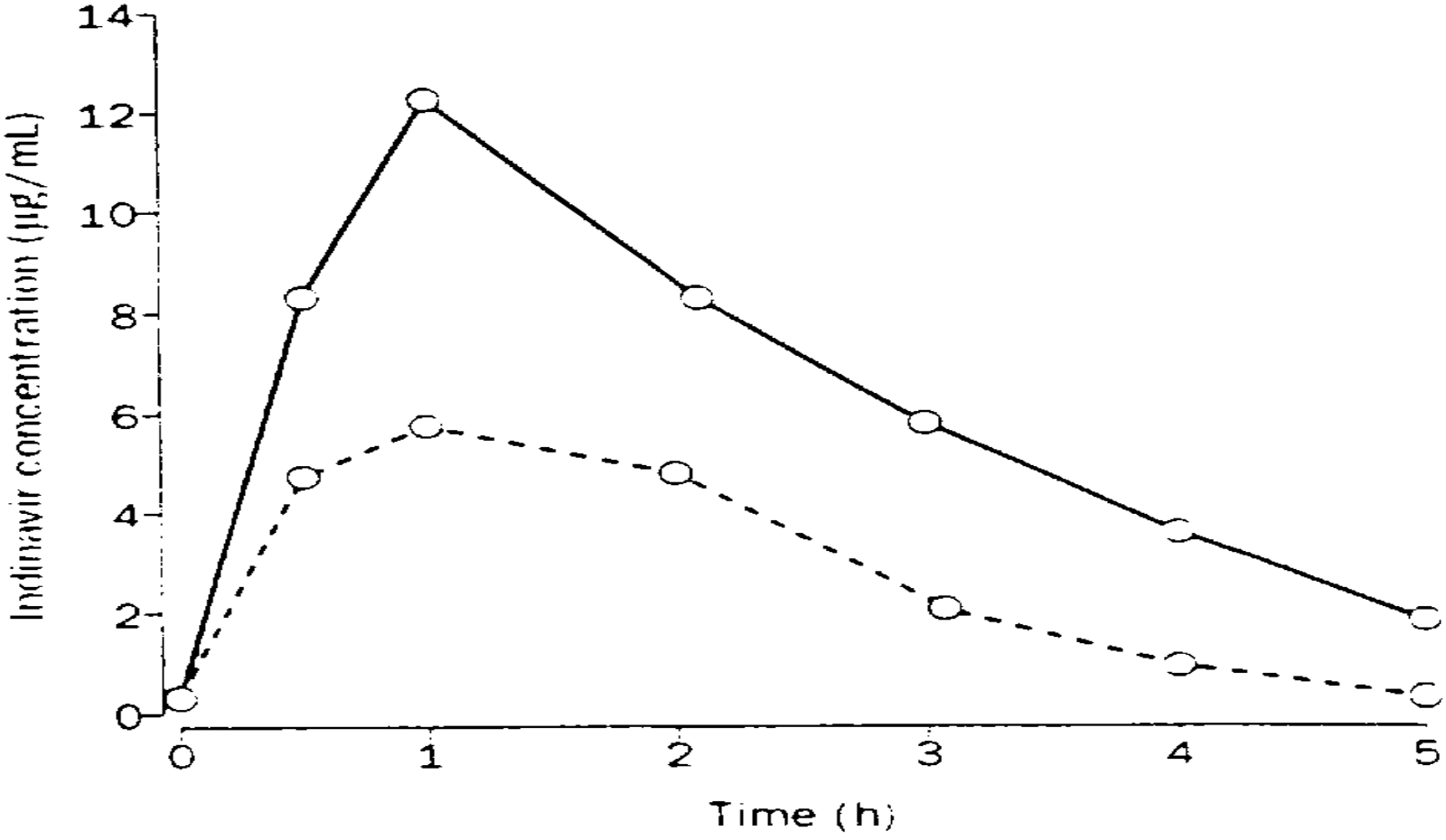
Dixon et al, 2000

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

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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 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

References

Agarwal DP, Goedde HW. Alcohol metabolism, alcohol intolerance and alcoholism: Biochemical and pharmacogenetic approaches. Berlin: Springer-Verlag; 1990

Ajir K, Smith M, Lin KM, et al. The pharmacokinetics and pharmacodynamics of adinazolam: multi-ethnic comparisons. Psychopharmacology. 129:265-270, 1997

Alfirevic A, Jorgensen AL, Williamson PR, Chadwick, WD, Park BK, Pirmobamed M. HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. Pharmacogenomics 7: 813, 2006

Allen JJ, Rack PH, Vaddadi KS. Differences in the effects of clomipramine on English and Asian volunteers: preliminary report on a pilot study. Postgrad Med J. 53(suppl 4):79-86, 1977

Alonso M, Val E, Rapaport MH. An open-label study of SSRI treatment in depressed Hispanic and non-Hispanic women. J Clin Psychiatry. 58:31, 1997

Bailey DG, Dresser GK, Bend JR. Bergamottin, lime juice, and red wine as inhibitors of cytochrome P450 3A4 activity: comparison with grapefruit juice. Clin Pharmacol Ther. 73:529-37, 2003

Binder RL, Levy R. Extrapyramidal reactions in Asians. Am J Psychiatry. 138:1243-1244, 1981

Binder RL, Kazamatusri H, Nishimura T, et al. Tardive dyskinesia and neuroleptic-induced parkinsonism in Japan. Am J Psychiatry. 144:1494-1496, 1987

Chen, P et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. New Eng J Med. 364:1126-1133, 2011

Chou WH, Yan FX, de Leon J, Barnhill J, Rogers T, Cronin M, Pho M, Xiao V, Ryder TB, Liu WW, Teiling C, Wedlund PJ. Extension of a pilot study: impact from the cytochrome P450 2D6 polymorphism on outcome and costs associated with severe mental illness. J Clin Psychopharmacol. 20:246-51, 2000

Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, Wu JY, Chen YT. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 428:486, 2004

Collazo Y, Tam R, Sramek JJ, Herrera J: Neuroleptic dosing in Hispanic and Asian inpatients with schizophrenia. Mt. Sinai Journal of Medicine 63:31-313, 1996

References

de Leon J, Armstrong SC, Cozza KL. The dosing of atypical antipsychotics. Psychosomatics. 46:262-73, 2005

Dixon LB, Sundquist J, Winkleby M. Differences in energy, nutrient, and food intakes in a US sample of Mexican-American women and men: findings from the Third National Health and Nutrition Examination Survey, 1988-1994. Am J Epidemiol. 152:548-57, 2000.

Dolder CR, Lacro JP, Dunn LB, et al: Antipsychotic medication adherence: is there a difference between typical an atypical agents. America Journal of Psychiatry 159:514, 2002

Edeki T. Clinical importance of genetic polymorphism of drug oxidation. Mt Sinai J Med. 63:291-300, 1996

Escobar JI, Tuason VB. Antidepressant agents: a cross-cultural study. Psychopharmacol Bll. 16:49-52, 1980

Fleishaker JC, Phillips JP. Adinazolam pharmacokinetics and behavioral effects following administration of 20-60mg oral doses of its mesylate salt in health volunteers. Psychopharmacol. 99:34-39, 1989

Gaviria M, Gil AA, Javaid JI. Nortriptyline kinetics in Hispanic and Anglo subjects. J Clin Psychopharmacol. 6:227-231, 1986

Glazer WM, Morgenstern H, Doucette J. Race and tardive dyskinesia among outpatients at a CMHC. Hosp Community Psychiatry. 45:38-42, 1994

Ghoneim MM, Korttila MK, Chian CK, et al. Diazepam effects and kinetics in Caucasians and Orientals. Clin Pharmacology and Therapeutics. 29:749-756, 1981

Gray GE, Pi EH: Ethnicity and Psychotropic Medication Related Movement Disorders. Journal of Practical Psychiatry and Behavioral Health 4:259-264, 1998

Gonzalez FJ: Human cytochromes P450: problem and prospects. Trends and Pharmacology Science Review, 13:346-352, 1992

References

Hamelin BA, Bouayad A, Drolet B, Gravel A, Turgeon J.In vitro characterization of cytochrome P450 2D6 inhibition by classic histamine H1 receptor antagonists. Drug Metab Dispos. 26:536-9 1998

Herbeck DM, West JC, Ruditis I, et al: Variations in use of second-generation antipsychotic medication by race among adult psychiatric patients. Psychiatric Service 55:677-684, 2004

Horrai Y, Nakano M, Ishizaki T, et al. Metoprolol and mephenytoin oxidation polymorphism in Far Eastern Oriental subjects: Japanese versus mainland Chinese. Clin Pharmaco Ther. 46:198-207, 1989

Jann MW, Lam YWF, Chang W-H. Haloperidol and reduced haloperidol plasma concentrations in different ethnic populations and interindividual variabilities in haloperidol metabolism. In: Lin K-M, Poland RE, Nakasaki G, eds. Psychopharmacology and Psychobiology of Ethnicity. Washington, DC: American Psychiatric Press:133-152, 1993

Jeste DV, Caligiuri MP, Paulsen JS. Risk of tardive dyskinesia in older patients: a prospective longitudinal study of 266 patients. Arch Gen Psychiatry. 52:756-765, 1995

Kalow W. Interethnic variation of drug metabolism. Trends Pharmaco Sci Rev.12:102-107,1991

Karno M, Ross RN, Caper RA. Mental health roles of physicians in a Mexican American community. Community Ment Health J. 5:62-69, 1969

Kishimoto A, Hollister LE. Nortriptyline kinetics in Japanese and Americans., J Clin Psychopharmacology. 4:171-172, 1984

Kleinman “A. Patients and Healers in the Context of Culture;: An exploration of the borderland between anthropology, medicine, and psychiatry. Berkeley: University of California Press; 1980

References

Kumana CR, Lauder IJ, Chan M, Ko W, Lin HF. Differences in diazepam pharmacokinetics in Chinese and white Caucasians: relation to body lipid stores. Eur J clin Pharmacol. 32:211-215, 1987

Kuno E, Rothbard AB: Racial disparities in antipsychotic prescription patterns for patients with schizophrenia. American Journal of Psychiatry 159:567-572, 2002

Kupfer A, Preisig R. Pharmacogenetics of mephenytoin: a new drug hydroxylation polymorphism in man. Eur J Clin Pharmacol. 26:753-759, 1984

Lawson WB: Racial and ethnic factors in psychiatric research. Hospital and Community Psychiatry 37:50-54, 1986

Lesser IM, Zisook, S, Flores D, et al. Depression outcomes of Spanish- and English-speaking Hispanic outpatients in STAR*D. Psychiatric Services 59:1273-84, 2008

Lesser IM, Myers HF, Lin KM, et al. Ethnic differences in antidepressant response: a prospective multi-site clinical trial. Depression & Anxiety 27:56-62, 2010

Lewis PO, Rack PH, Vaddadi KS, et al. Ethnic differences in drug response. Postgrad Med J. 56(suppl 1):46-49, 1980

Lilja, JJ, Kivisto KT, Neovonen PJ. Grapefruit juice-simvastatin interactions: Effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors. Clin Pharmacol Ther 64: 477-83,1998

Lim, K.S., Kwan, P., and Tan, C.T. Association of HLA-B1502* allele and carbamazepine-induced severe adverse cutaneous drug reaction among Asians, a review. Neurol. Asia 13:15-21 2008

Lin KM, Innui TS, Kleinman A, Womack W. Sociocultural determinants of the help-seeking behavior of patients with mental illness. J Nerv Ment Dis. 170:78-85, 1982

References

Lin KM, Finder E: Neuroleptic dosage for Asians. American Journal of Psychiatry 140:490-491, 1983

Lin KM, Poland RE,, Lau JK, et al. Haloperidol and prolactin concentrations in Asians and Caucasians. J Clin Psychopharmaclogy. 8:195-201, 1988

Lin KM, Lau J, Smith R, et al. Comparison of alprazolam plasma levels and behavioral effects in normal Asian and Caucasian male volunteers. Psychopharmacology. 96:365-369, 1988

Lin KM, Poland RE, Nuccio I, et al: A longitudinal assessment of haloperidol dose and serum concentrations in Asian and Caucasian schizophrenic patients. American Journal of Psychiatry 146:1307-1311, 1989

Lin K-M, Poland "RE, Chang S, Chang W-H. Psychopharmacology for the Chinese: cross-ethnic perspectives. In: Lin TY, Tsent WS, Yeh EK, eds. Chinese Societies and Mental Health. Hong Kong: Oxford University Press; 308-314, 1995

Livingston RL, Zucker DK, Isenberg K, Wetzel RD. Tricyclic antidepressants and delirium. J Clin Psychiatry. 44:173-176, 1983

Lown KS, Bailey DG, Fontana RJ, Janardan SK, Adair CH, Fortlage LA, Brown MB, Guo W, Watkins PB. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. J Clin Invest. 99(10):2545-53. 1997

Lu FG, Chien C-P, Heming G, Hinton, L., Soussain, C. Ethnicity and Neuroleptic drug dosage. Poster Presentation, Annual Meeting of the American Psychiatric Association. Chicago, IL., May 12. 1987

References

Malhotra S, Bailey DG, Paine MF, Watkins PB. Seville orange juice-felodipine interaction: comparison with dilute grapefruit juice and involvement of furocoumarins. Clin Pharmacol Ther. 69:14-23, 2001

Manson SM, Walker RD, Kivlahan DR. Psychiatric assessment and treatment of American Indians and Alaska natives. Hosp. Community Psychiatry 38: 165-173, 1987

Marcos LR, Cancro R. Pharmacotherapy of Hispanic depressed patients: clinical observations. Am J Psychother. 36:505-513, 1982

Matsuda KT, Cho MC, Lin KM, Smith MW, Young AS, Adams JA. Clozapine dosage, serum levels, efficacy, and side-effect profiles: a comparison of Korean-American and Caucasian patients. Psychopharmacol Bull.32:253-7, 1996

Melfi CA, Croghan TW, Hanna MP, et al: Racial variation in antidepressant treatment in a Medicaid population. Journal of Clinical Psychiatry 61:16-21, 2000 Mezzich JE, Raab ES. Depressive symptomatology across the Americas. Arch Gen Psychiatry. 37:818-823, 1980

Mendoza R, Smith MW, Poland RE, et al: Ethnic psychopharmacology: the hispanic and native American perspective. Psychopharmacol Bull. 27:449-461, 1991

Mihara K, Suzuki A, Kondo T, Yasui N, Furukori H, Nagashima U, Otani K, Kaneko S, Inoue Y. Effects of the CYP2D6*10 allele on the steady-state plasma concentrations of haloperidol and reduced haloperidol in Japanese patients with schizophrenia. Clin Pharmacol Ther. 65:291-4, 1999

Morita S, Shimoda K, Someya T, Yoshimura Y, Kamijima K, Kato N. Steady-state plasma levels of nortriptyline and its hydroxylated metabolites in Japanese patients: impact of CYP2D6 genotype on the hydroxylation of nortriptyline. J Clin Psychopharmacol. 20:141-9 2000

References

Mucklow JC, Fraser HS, Bulpitt CJ, et al. Environmental factors affecting paracetamol metabolism in London factory and office workers. Br J Clin Pharmacol. 10:67-70, 1980

Mukherjee MD, Shukla S, Woodle J, Rosen AM, Olarte S. Misdiagnosis of schizophrenia bipolar patients: a multiethnic comparison. Am J Psychiatry. 140:1571-1574, 1983

Nicolas JM, Whomsley R, Collart P, Roba J. In vitro inhibition of human liver drug metabolizing enzymes by second generation antihistamines.Chem Biol Interact. 1999 Nov 15;123(1):63-79.

Palma-Aguirre JA, Nava Rangel J, Hoyo-Vadillo C, Girard-Cuesy ME, Castaneda-Hernandez G, Arteaga-Granados E, De Mucha-Macias R. Influence of Mexican diet on nifedipine pharmacodynamics in healthy volunteers. Proc West Pharmacol Soc. 1994;37:85-6.

Phillips KA, Mayer ML, Aday LA: Barriers to care among racial/ethnic groups under managed care. Health Affairs 19:65-75, 2000

Pi EH, Simpson GM, Cooper TB. Pharmacokinetics of desipramine in Caucasian and Asian volunteers. Am J Psychiatry. 143:1174-1176, 1986

Pi EH, Tran-Johnson TK, Walker NR, et al. Pharmacokinetics of desipramine in Asian and Caucasian volunteers. Psychopharmacol Bull. 25:483-387, 1989

Pi EH, Tran-Johnson TK, Gray GE, et al. Saliva and plasma desipramine levels in Asian and Caucasian volunteers. Pschopharmacol Bull. 27:281-284, 1991

Pi EH, Wang AL, Gray GE. Asian/non-Asian transcultural tricyclic antidepressant psychopharmacology: a review. Prog Neuropsychopharmacol Biol Psychiatry. 17:691-702, 1993

Pi EH, Gray GE: A Cross-cultural perspective on psychopharmacology. Essential Psychopharmacology 2:233-262, 1998

References

Pi EH and Simpson GM: Cross-Cultural Psychopharmacology: A Current Clinical Perspective. Journal of Psychiatric Services, 56:31-33, 2005

Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort. Lancet. 355:547-8, 2000

Potkin SB, Shen Y, Pardes H, et al. Haloperidol concentrations elevated in Chinese patients. Psychiatric Research. 12:167-172, 1984

Price N, Glazer W, Morgenstern H: Demographic predictors of the use of injectable versus oral antipsychotic medications in outpatients. American Journal of Psychiatry 142:1491-1492, 1985

Qin XP, Xie HG, Wang W, He N, Huang SL, Xu ZH, Ou-Yang DS, Wang YJ, Zhou HH. Effect of the gene dosage of CgammaP2C19 on diazepam metabolism in Chinese subjects. Clin Pharmacol Ther. 66:642-6, 1999

Ramirez LF. Ethnicity and psychopharmacology in Latin America. Mt Sinai J Med. 63:330-331, 1996

Raskin A, Thomas H, Crook MA. Antidepressants in black and white inpatients. Arch Gen Psychiatry. 32:643-649, 1975

Reen RK, Roesch SF, Kiefer F, Wiebel FJ, Singh J. Piperine impairs cytochrome P4501A1 activity by direct interaction with the enzyme and not by down regulation of CYP1A1 gene expression in the rat hepatoma 5L cell line. Biochem Biophys Res Commun. 218:562-9, 1996

Reggiani K, Vandel P, Haffen E, Sechter D, Bizouard P, Vandel S. Extrapyramidal side effects of neuroleptic and antidepressant treatment: assessment of potential risk factors through CYP2D6 genetic polymorphism Encephale. 26:62-7, 2000

References

Richelson E. Pharmacokinetic drug interactions of new antidepressants: a review of the effects on the metabolism of other drugs Mayo Clin Prc. 72:835-847,1997

Rudorfer MV, Robins E. Amitriptyline overdose: clinical effects on tricyclic antidepressant plasma levels. J Clin Psychiatry. 43:457-460, 1982

Rudorfer MV, Lane EA, Chang WH, et al. Desipramine pharmacokinetics in Chinese and Caucasian volunteers. Br J Clin Pharmacology. 17:433-440, 1984

Rudorfer MV, Lane EA, Potter WZ. Interethnic dissociation between debrisoquine and desipramine hydroxylation. J Clin Pharmacology. 5:89-92, 1985

Ruiz S, Chu P, Sramek J, Rotavi E, Herrera J. Neuroleptic dosing in Asian and Hispanic outpatients with schizophrenia. Mt Sinai J Med. 63:306-309, 1996

Segal SP, Bola JR, Watson MA: Race, quality of care, and antipsychotic prescribing practices in psychiatric emergency services. Psychiatric Services 47:282-286. 1966

Sjoqvist F, Borga AO, Dahl M-L, Orme MLE. Fundamentals of clinical pharmacology. In: Speight TM, Holford NHG, eds. Avery's drug Treatment. 4th ed. Auckland: ADIS International 1-73, 1997

Smith M, Lin K-M, Mendoza R. "Nonbiological" issues affecting psychopharmacology: cultural considerations. In: Lin K-M, Poland "Re, Nakasaki G, eds. Psychopharmacology and Psychobiology of Ethnicity. Washington, DC: American Psychiatric Press. 37-60, 1993

Smith MW; Etnopsicofarmacologia en América Latina. In Alarcon R, Mazzotti G, Nicolini H (Eds) Psiquiatria 2nd Edición Manual Moderno, México DF 2005

References

Sowunmi A, Rashid TJ, Akinyinka OO, Renwick AG. Ethnic differences in nifedipine kinetics: comparisons between Nigerians, Caucasians and South Asians. Br J Clin Pharmacol. 1995 Nov;40(5):489-93.

Sramek JJ, Sayles MA, Simpson GM: Neuroleptic dosage for Asians: a failure to replicate. American Journal of Psychiatry 143:5535-536, 1986

Sramek JJ, Roy S, Ahrens T, et al. prevalence of tardive dyskinesia among three ethnic groups of chronic psychiatric patients. Hosp Community Psychiatry. 42:590-592, 1991

Strickland TL, Lin K-M, Fu P, Anderson D, Zheng Y. Comparison of lithium ratio between African-American and Caucasian bipolar patients. Biol Psychiatry. 37:325-330, 1995

Zhou HH, Koshakji RP, Siberstein DJ, Wilkinson GR, Wood AJ. Altered sensitivity to and clearance of propranalol in men of Chinese descent as compared with American Whites. N Engl J Med. 320:565-570, 1989

Zhou HH, Adedoyin A, Wilkinson GR: Differences in plasma binding of drugs between Caucasians and Chinese subjects. Clinical Pharmacology and Therapeutics. 48:10-17, 1990

Zhou S, Yung Chan S, Cher Goh B, Chan E, Duan W, Huang M, McLeod HL. Mechanism-based inhibition of cytochrome P450 3A4 by therapeutic drugs. Clin Pharmacokinet.44:279-304, 2005

Ziegler VE, Biggs TE. Tricyclic plasma levels-effect of age, race, sex, and smoking. JAMA. 238:2167-2169, 1977 Segal SP, Bola JR, Watson MA: Race, quality of care, and antipsychotic prescribing practices in psychiatric emergency services. Psychiatric Services 47:282-286. 1966