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

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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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 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

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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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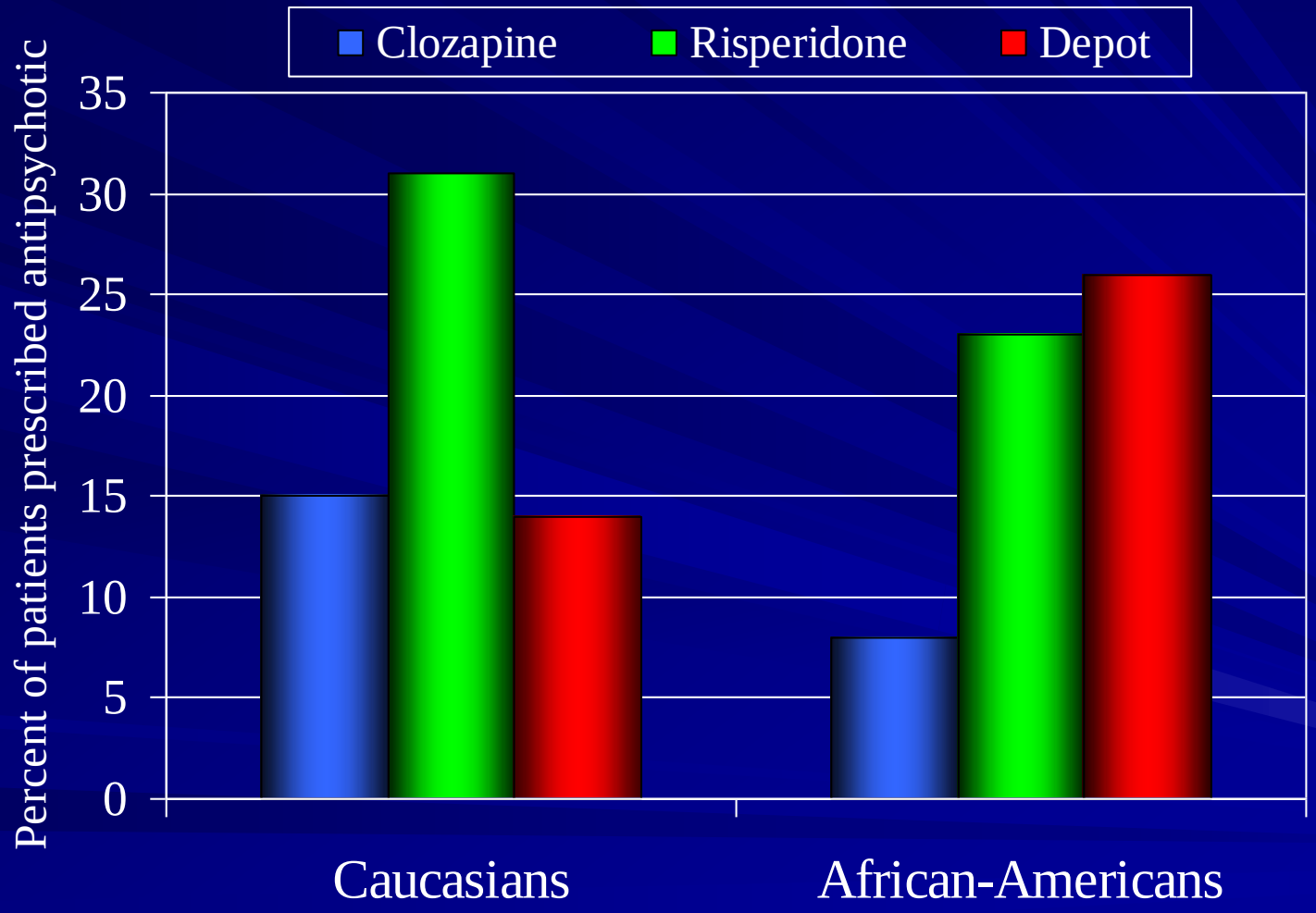
American Indians and Alaska Natives

- 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

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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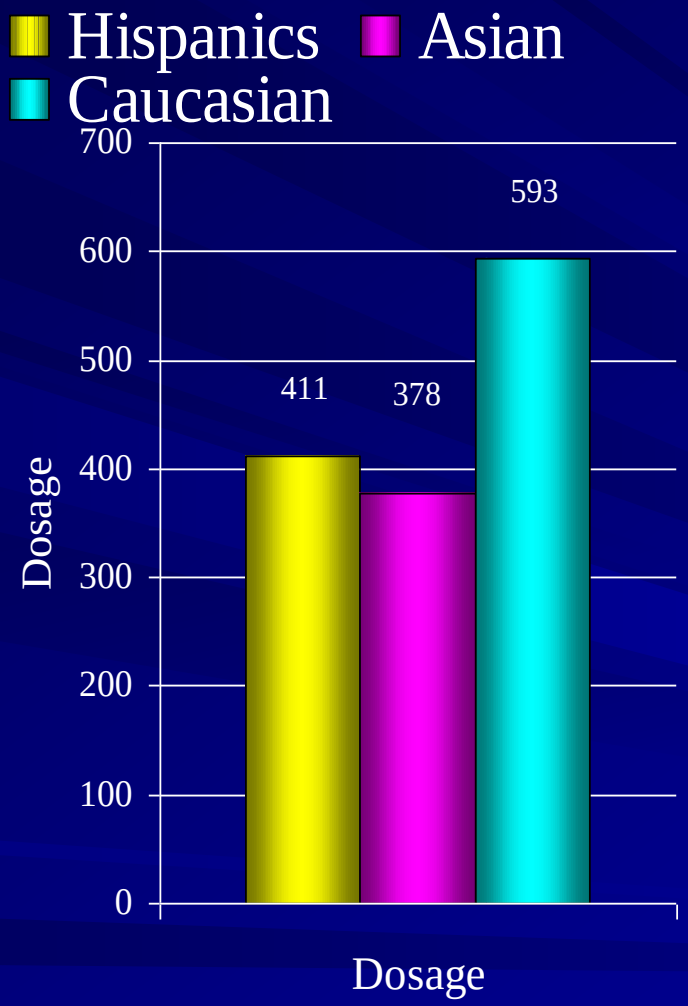
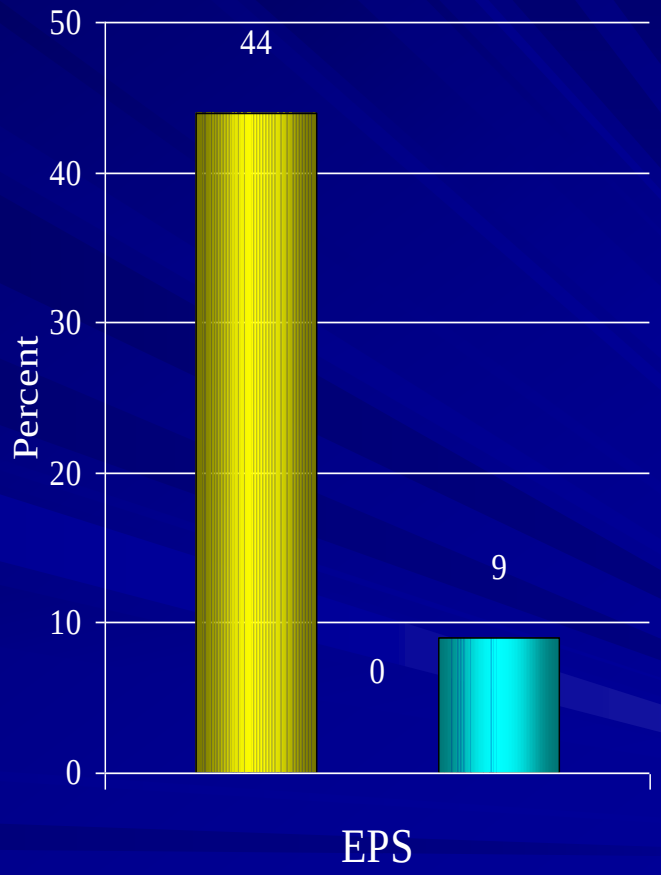
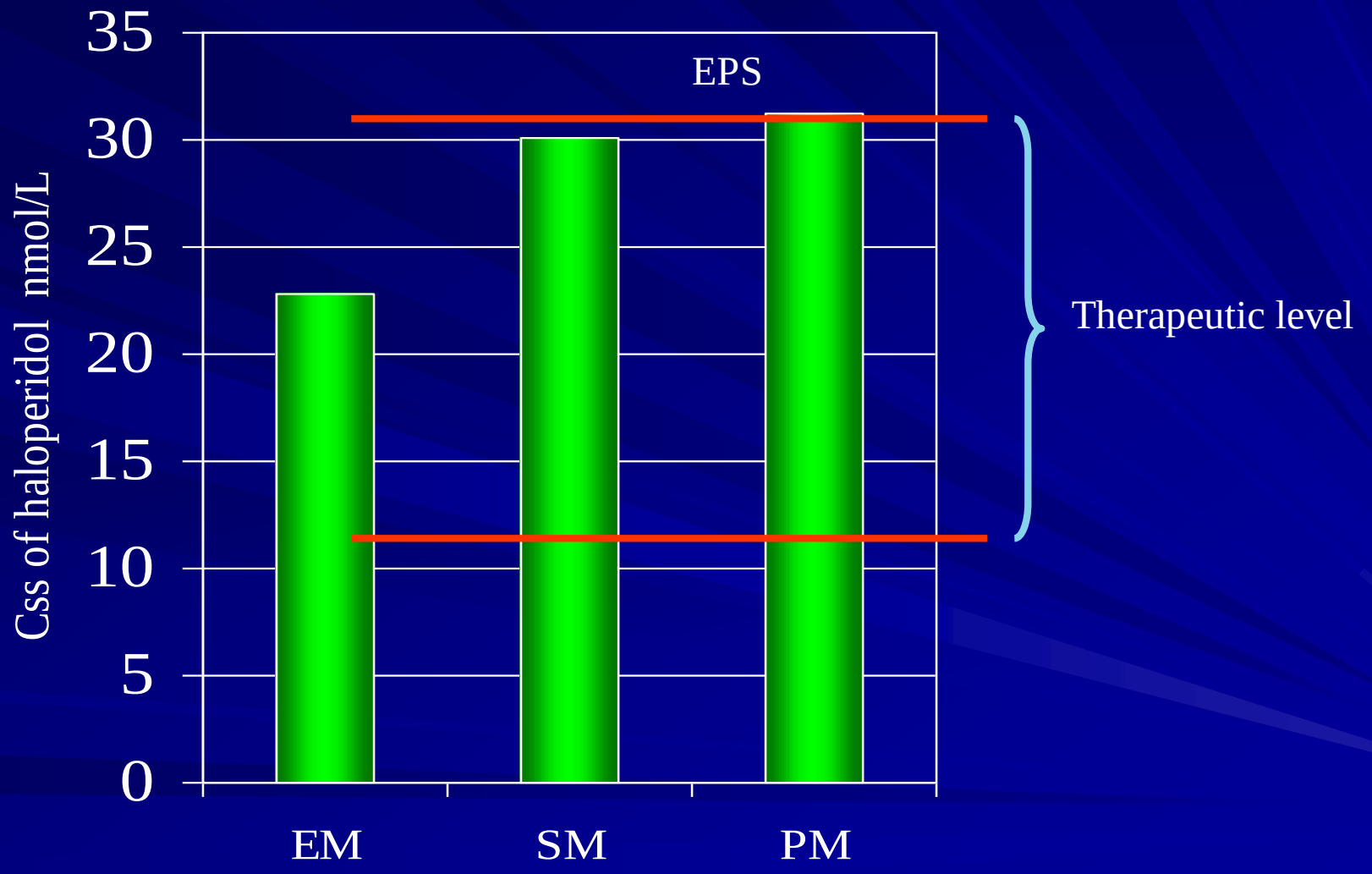
Antipsychotics: Collazo et al 1996



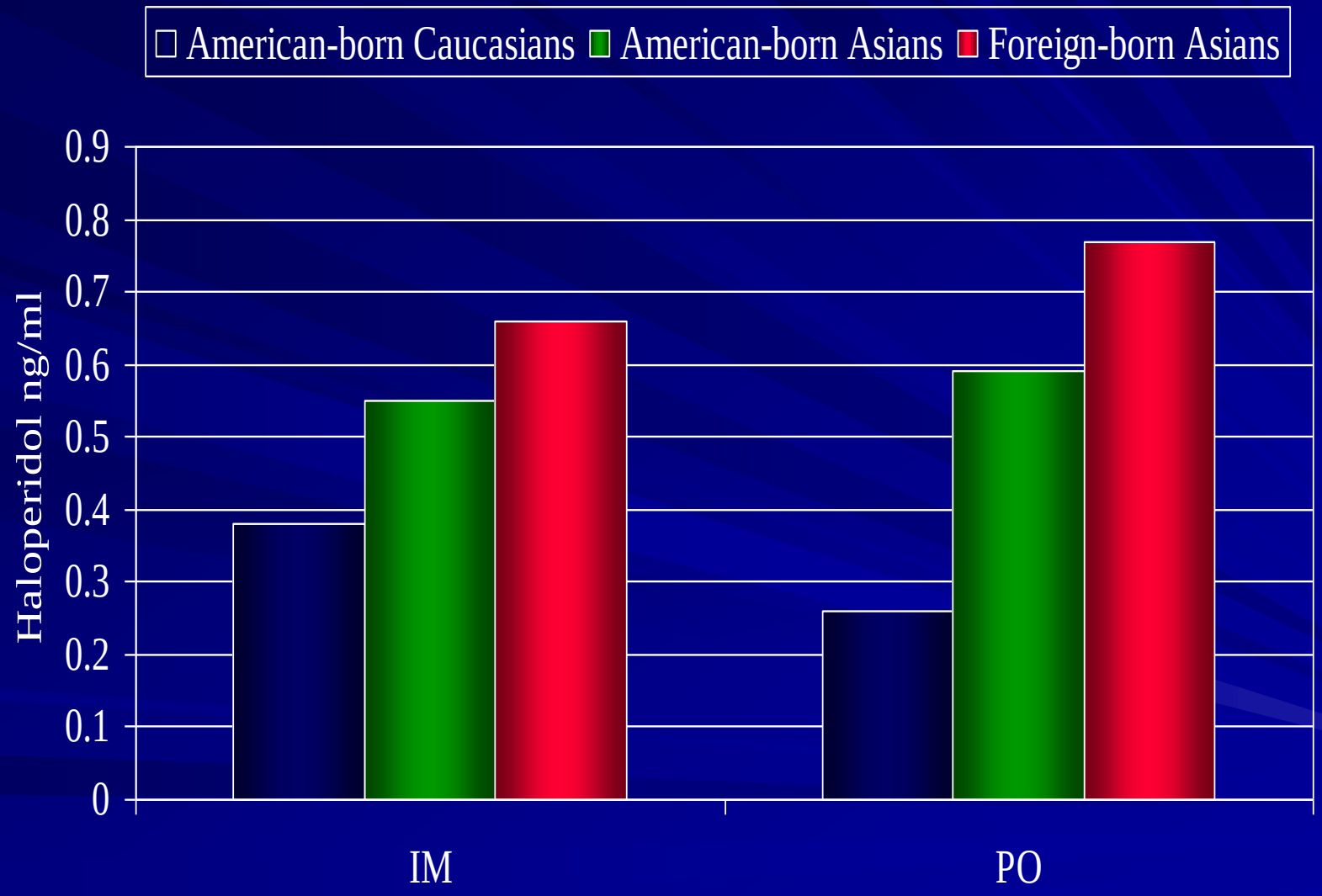


Asian Americans: Antipsychotics
Haloperidol and the CYP2D6*10 allele



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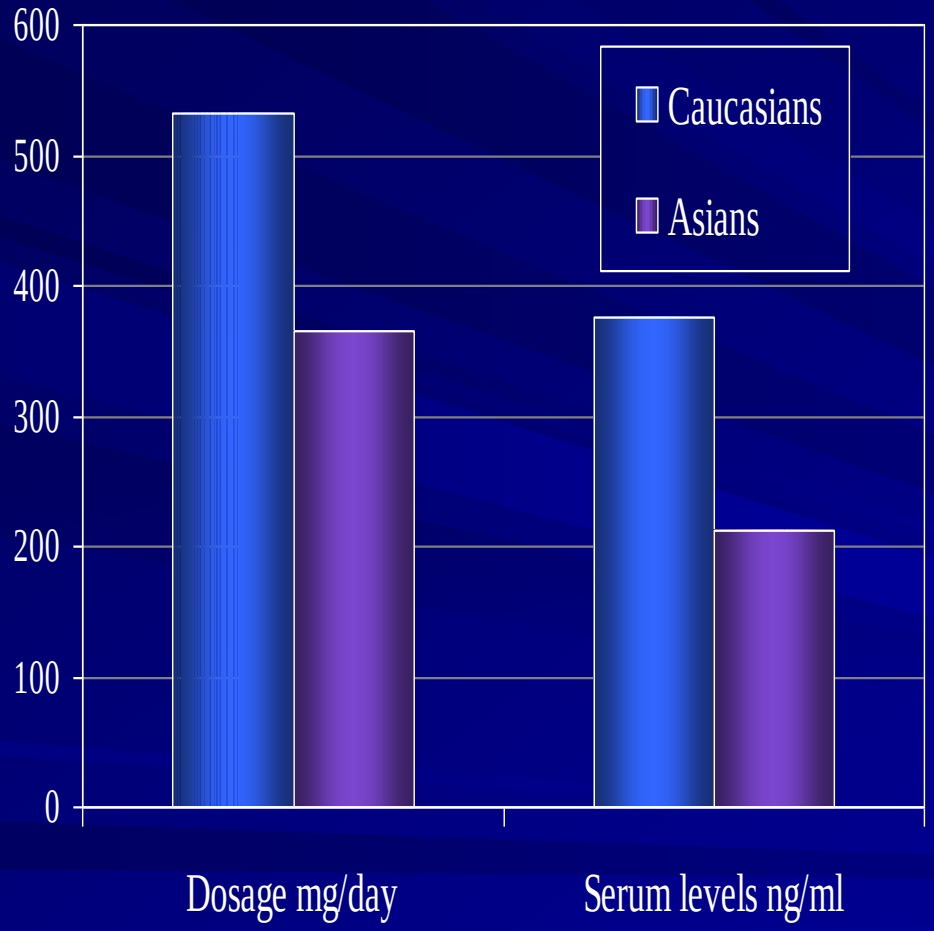
Asian Americans: Antipsychotics
Clozapine: Dosage, Serum Levels, & Response



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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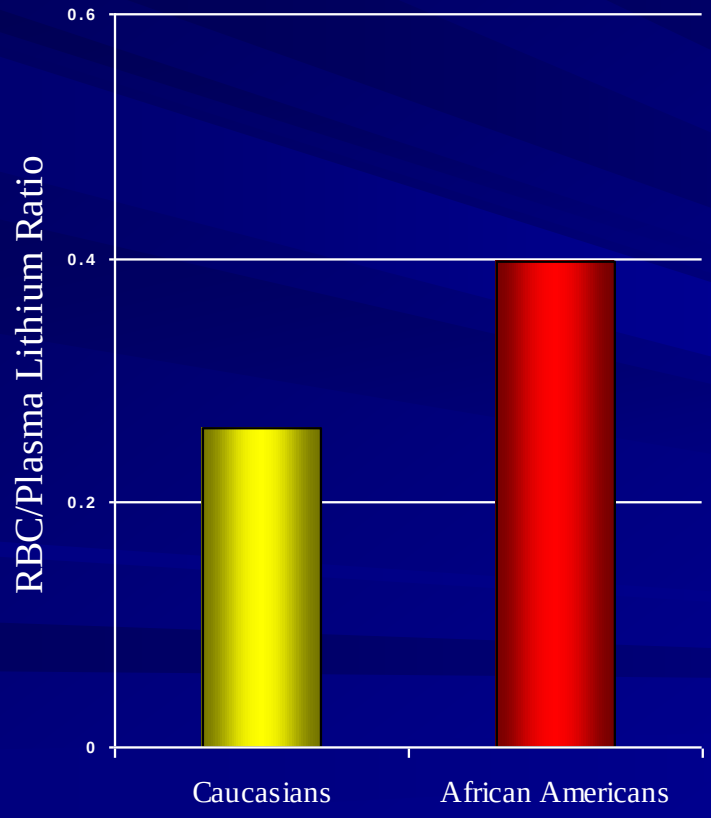
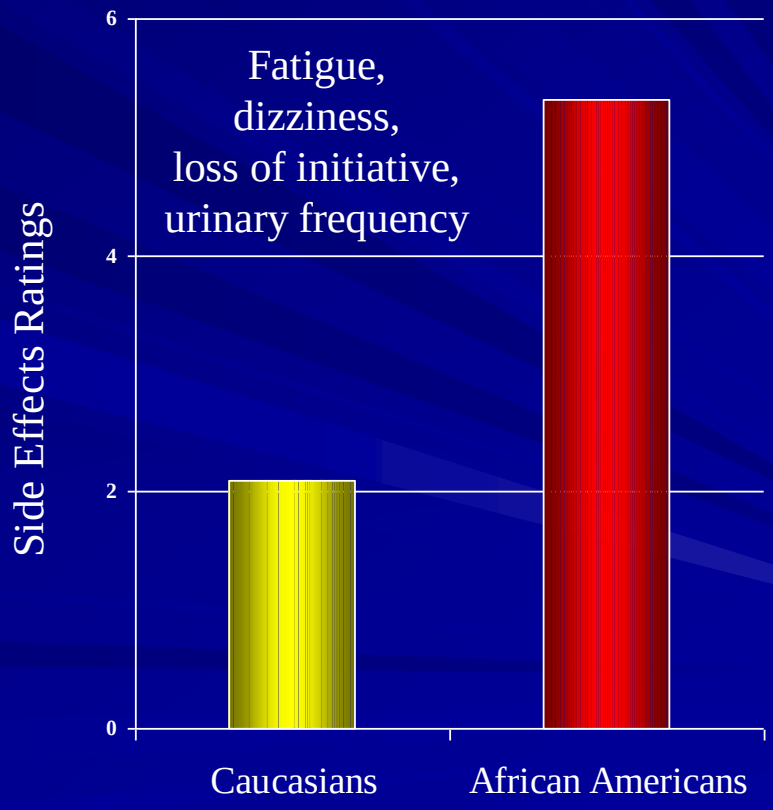
RBC Lithium counter transport associated with side effects in African Americans

RBC/Plasma Lithium Ratio: Ethnic Variation

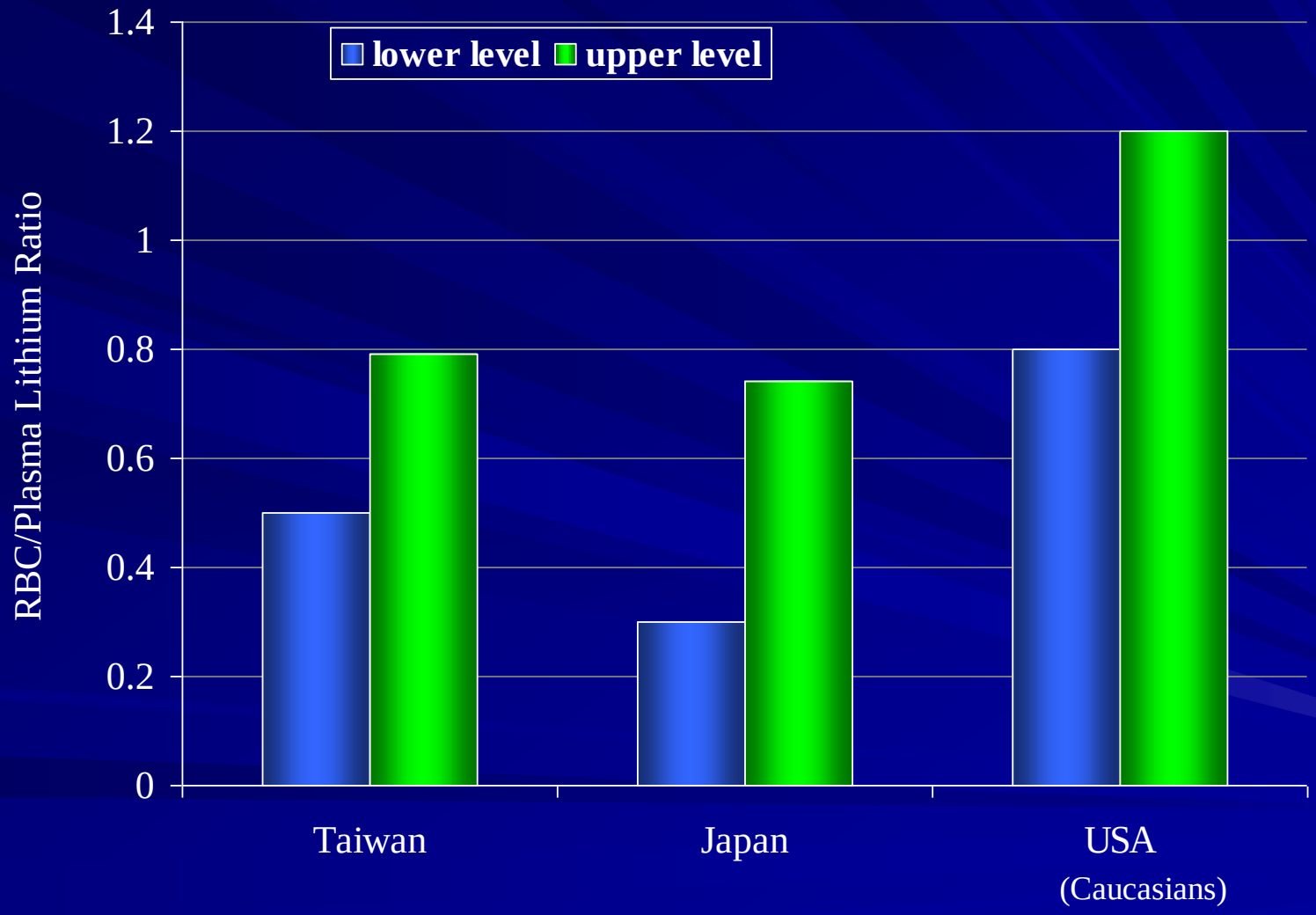


Lithium Side Effects Ratings: Ethnic Variation



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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Asian Americans
Carbamazepine induced skin hypersensitivity

- 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.

Chung et al, 2004; Alfirevic et al, 2006

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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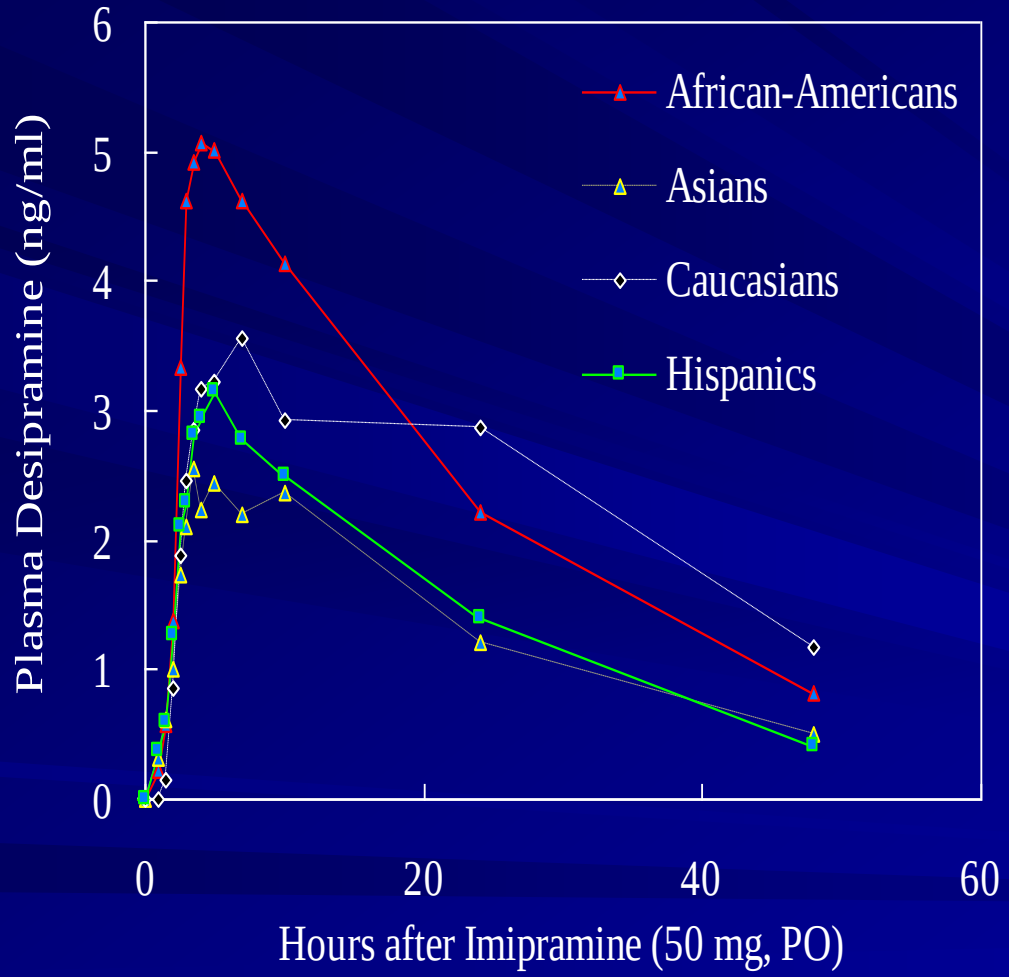
Ethnic Variation in Imipramine Metabolism



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

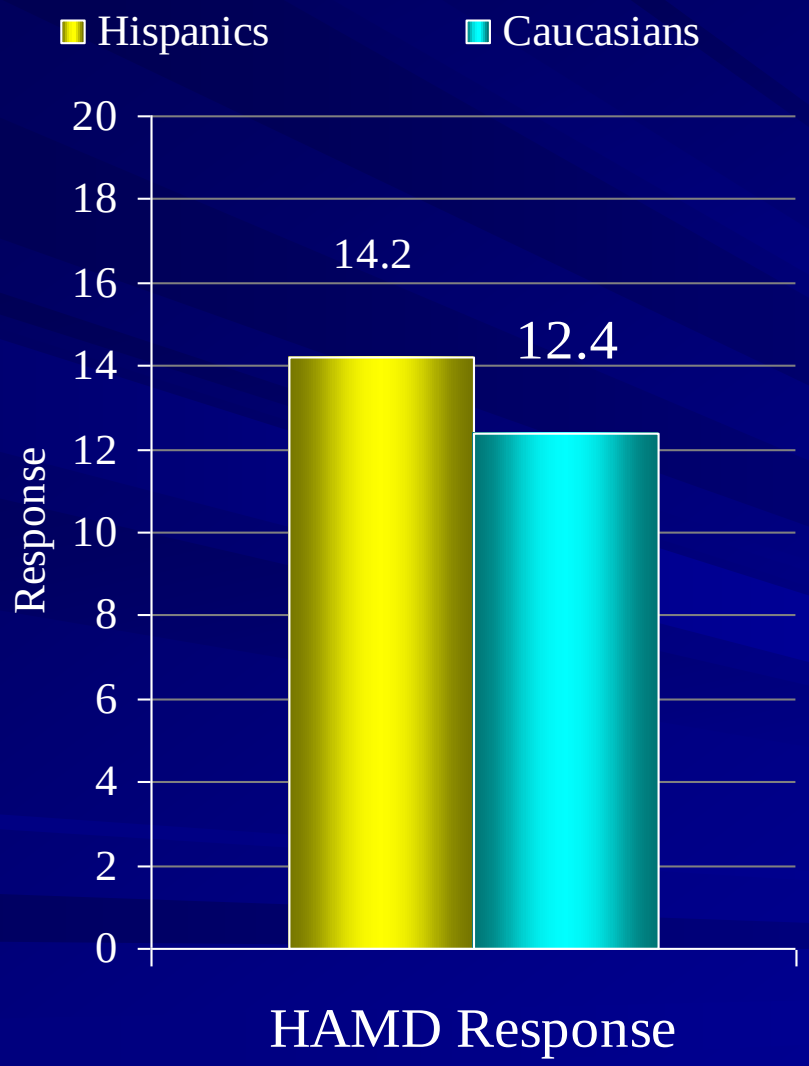
Mezzich & Raab, 1980; Marcos & Cancro, 1982; Escobar & Tuason, 1980; Gaviria et al, 1986 *

Hispanics: Antidepressants
Marcos and Cancro 1982

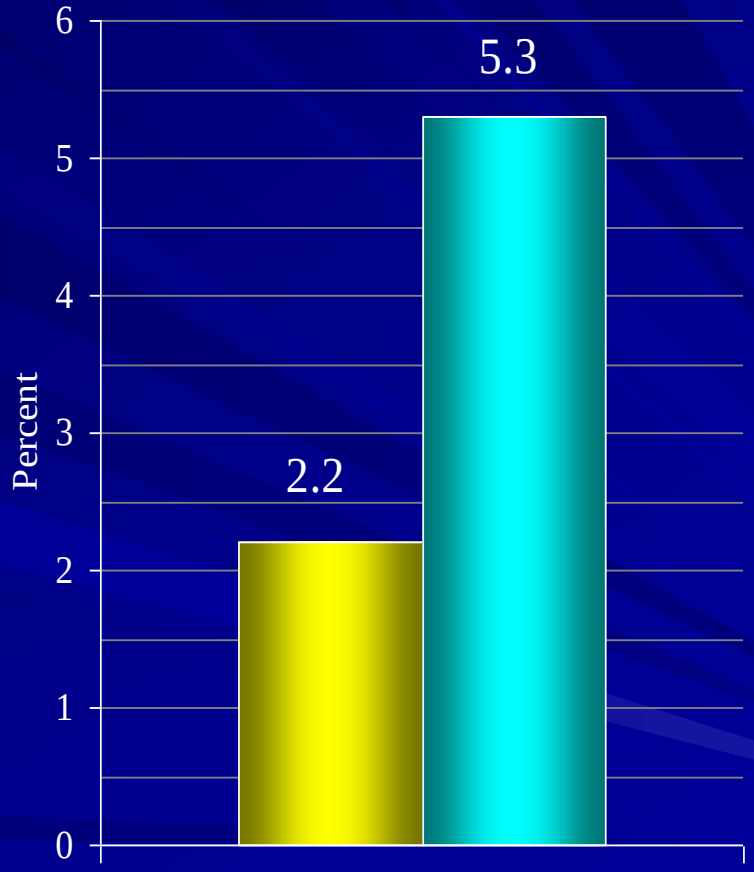
41 Hispanic (PR) and 21 Caucasian female outpatients

- 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

*

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

*

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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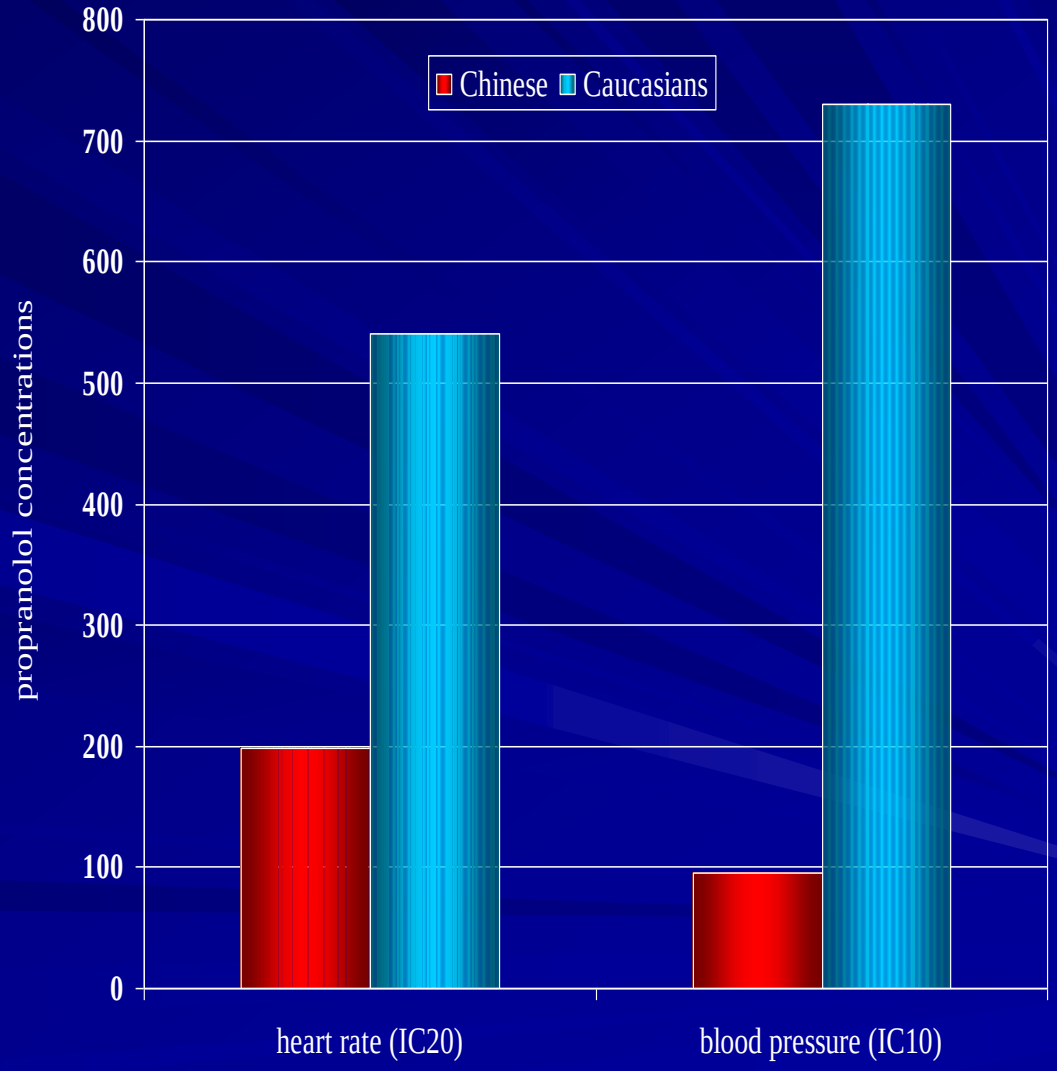
Propranalol Response: Chinese vs. Caucasians

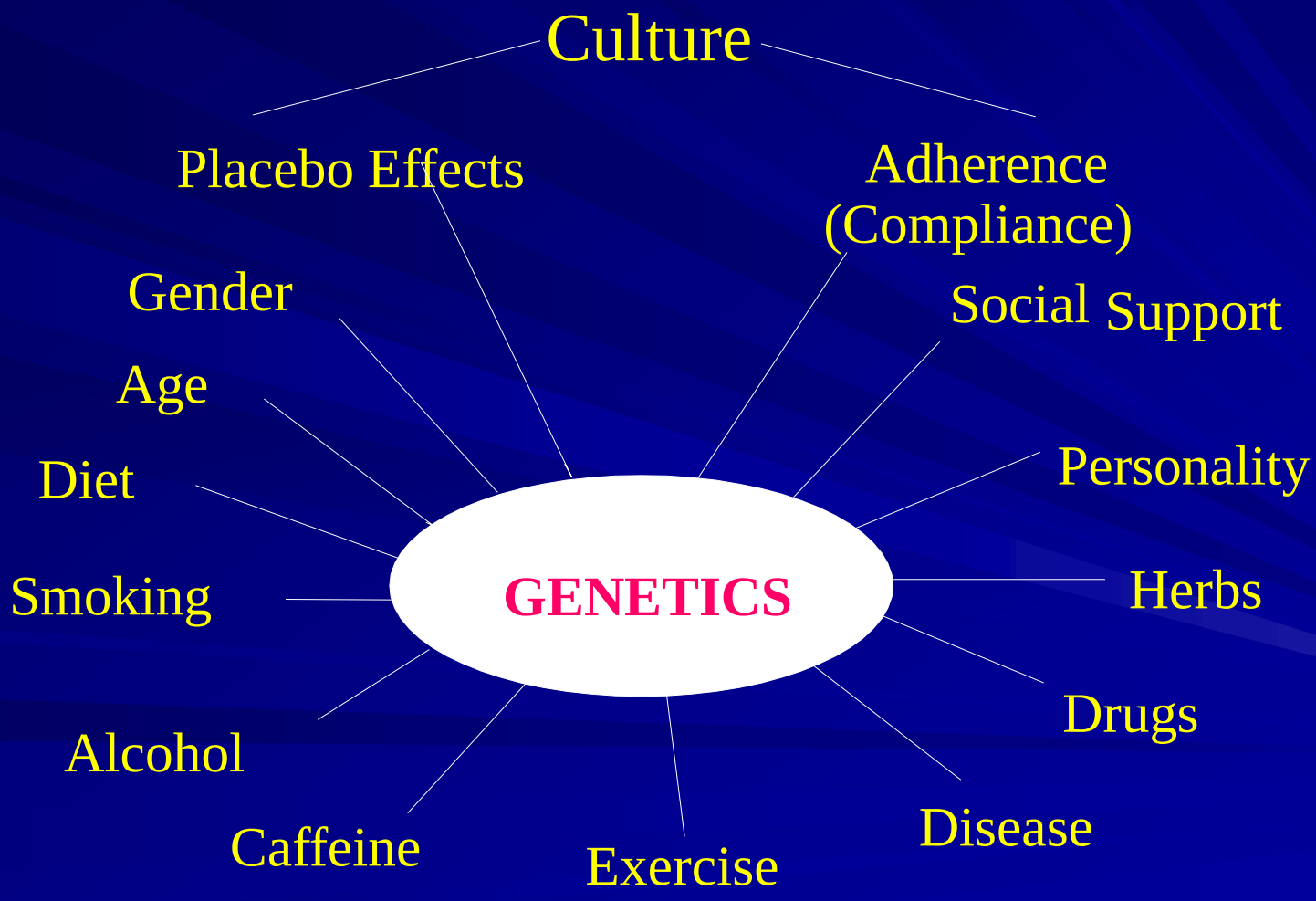
b-blocker propranalol

•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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