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) than 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
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.
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
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
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

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

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

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
Asian Americans: Antipsychotics

Haloperidol and the CYP2D6*10 allele

Milhard et al, 1999
Asian Americans: Antipsychotics
Haloperidol: Lin et al. 1988

- American-born Caucasians
- American-born Asians
- Foreign-born Asians

Bar chart showing the levels of Haloperidol ng/ml for different groups of Asian Americans.
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
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
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
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*
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
RBC Lithium counter transport associated with side effects in African Americans

RBC/Plasma Lithium Ratio: Ethnic Variation

Lithium Side Effects Ratings: Ethnic Variation

Fatigue, dizziness, loss of initiative, urinary frequency

Asians: Therapeutic Lithium Levels:

Yang 1985

(Caucasians)
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
Hispanic Americans
Lithium

Lithium

- Bipolar patients may be misdiagnosed as schizophrenia

- Pharmacokinetics and RBC/plasma lithium ratio: ?

Mukherjee et al, 1983
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

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.
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
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% discontinued TCA
- Caucasians: 33% discontinued TCA
Hispanics: Antidepressants
SSRI’s: Alonso et al 1997

Hispanics | Caucasians
---|---
14.2 | 12.4

HAMD Response

Side Effects*

Percent

* = 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
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
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 adverse 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

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
b-blocker propranalol

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

Zhou et al, 1989
Factors Affecting Drug Response

Culture
- Placebo Effects
- Gender
- Age
- Diet
- Smoking
- Alcohol
- Caffeine
- Exercise

GENETICS

Adherence (Compliance)
- Social Support
- Personality
- Herbs
- Drugs
- Disease

Factors Affecting Drug Response

Culture
- Placebo Effects
- Gender
- Age
- Diet
- Smoking
- Alcohol
- Caffeine
- Exercise

GENETICS
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 \( \alpha_1 \)-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
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
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
Cytochrome P450 (CYP) Enzymes

- Enzyme systems that are responsible for metabolizing most psychotropic medications

- Genetic polymorphism
  - Super Extensive metabolizers (SEM's)
  - Extensive metabolizers (EMs)
  - Poor metabolizers (PMs)
  - Slow metabolizers (SM's)

- Can be induced by specific substrates:
  - phenobarbital, ethanol, and steroids

- Can also be inhibited by various medications that are potent competitive inhibitors of the enzymes:
  - cimetidine and ketoconazole

Richelson 1997; Sjoqvist et al, 1997; Gonzalez 1992; Kalow 1991
P450 Enzyme System involved in Psychotropic metabolism

- CYP 1A2  
  Drug metabolism

- CYP 2A6  
  Nicotine metabolism

- CYP 2C19  
  Drug metabolism

- CYP 2D6  
  Drug metabolism

- CYP 2E1  
  Alcohol metabolism

- CYP 3A3/4  
  Drug metabolism

Adapted from Smith 2005
CYP2D6
(Debrisoquin hydroxylase)

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

Richelson 1997; Sjoqvist et al, 1997; Edeki 1996; Sjoqvist et al, 1997
CYP2D6 Substrates

- **Antipsychotics** - haloperidol*, reduced haloperidol, perphenazine, phenothiazines*, thioridazine*, olanzapine*, risperidone*, sertindole*

- **Antidepressants** - amitryptiline*, desipramine, imipramine*, nortryptilene, trazodone, fluoxetine, paroxetine, venlafaxine

- **Cardiovascular Agents** - encanide, flecanide, propanalol*, metropolol, timolol

- **Opiates** - codeine*, dexamethorphan, hydrocodone*

* Adapted from Smith 2005
Distribution of CYP2D6 Activity in Caucasian Populations

Number of subjects

MR = 12.6
CYP2D6 Poor Metabolizers

Adapted from Smith 2005
# CYP2D6 Metabolic Rates

<table>
<thead>
<tr>
<th>Metabolic type</th>
<th>Rate of metabolism</th>
<th>Plasma Drug levels</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PM</strong> Poor metabolizer</td>
<td>No metabolism</td>
<td>Toxic drug levels</td>
<td>Side effects</td>
</tr>
<tr>
<td><strong>EM</strong> Extensive metabolizer</td>
<td>Normal metabolism</td>
<td>Normal drug level</td>
<td>Normal response</td>
</tr>
</tbody>
</table>

Adapted from Smith 2005
Ethnic Variation in CYP2D6 Activity

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.

Debrisoquine/4-hydroxy-debrisoquine metabolic ratio
# CYP2D6 Metabolic Rates

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</thead>
<tbody>
<tr>
<td><strong>IM</strong> Intermediate</td>
<td>Slow metabolism</td>
<td>High drug levels</td>
<td>Side effects—higher</td>
</tr>
<tr>
<td>metabolizer</td>
<td></td>
<td></td>
<td>dose</td>
</tr>
<tr>
<td><strong>UM</strong> Ultra</td>
<td>Super fast metabolism</td>
<td>Low or no drug level</td>
<td>No response at normal</td>
</tr>
<tr>
<td>metabolizer</td>
<td></td>
<td></td>
<td>doses</td>
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</table>

Adapted from Smith 2005
CYP2D6 Poor & Intermediate Metabolizers

- African American: 33%
- Asian Americans: 37%
- Caucasian: 7.3%
- Mexican American: 3.1%
- Nicaraguans: 3.6%

Percent poor & slow metabolizers in population

PM IM

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

CYP2D6 Ultra Metabolizers

Adapted from Smith 2005
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

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

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, propranolol, riluzole, ropivacaine, theophylline, tacrine, zileuton, zolmitriptan

Adapted from Smith 2005
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, Atkins 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, Tribestronie II, Ultra Chondroitin 600

Reen et al, 1996
Smoking and Antipsychotic Response

Percent decrease in serum levels due to CYP1A2 induction via smoking

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
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, ketoconazole, nelfinavir, saquinavir, ritonavir, taxol*, tamoxifen, vincristine
- alfentanil, astemizole, 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
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.

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

Flushing
Fainting
Intense HA
Moderate HA
Sleepy
Dizzy
Drowsiness
Slight HA

Palma-Aguire, 1999
Diet Variation, Migration & Acculturation Among Mexican American Women

Dixon et al, 2000
Citrus Aurantium Containing Supplements

- Citrus Aurantium which is used in both Chinese and Hispanic herbal medicine has been found to be a stronger inhibitor of CYP3A4 than Grapefruit juice.

- Acutrim Natural A.M., Adrenerlin, Allergia, Allergy Relief, Athletica, Citraterm, 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

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

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
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
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
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
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) than 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
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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