Ethnopharmacology
Understanding Differences in Drug Response Based on Race/Ethnicity?

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Objectives
Upon completion of this session, the participant should be able to:

1. Conceptually differentiate between race, ethnicity and culture in relation to ethnopharmacology.
2. Identify at least two ethnic/racial differences in response to medications.
3. State at least one strategy to improve clinical practice as a result of heightened awareness of ethnopharmacology.
What is Ethnopharmacology?

Potentially Confusing Terms

- Ethnic pharmacology
- Ethnomedicine
- Transcultural Pharmacology
- Culturally Competent Pharmacology
- Pharmacogenetics
- Pharmacogenomics
Ethnopharmacology: Definitions

• The field of study that investigates the impact culture, environment, genetics, biophysiology and psychosocial factors have on prescribing, metabolism of and response to medications

• The field addressing important implications of genetics, environment and culture as these relate to pharmacodynamics

• The study of the effect of ethnicity on responses to prescribed medication, drug absorption, metabolism, distribution and secretion

Ethnopharmacology

The study of racial differences in drug metabolism and response

(Campinha-Bacote, 2007)

(Munoz & Hilgenberg, 2005; Wynne et al., 2007)
Ethnopharmacology: Key Concepts

- Race
- Ethnicity
- Culture

Race

- A genetically-based classification usually based on individual physical features
- An ethnic stock or division of humans

(Merriam-Webster, 2008; medicine.net.com, 2008)
**Ethnicity**

- Pertaining or relating to a group or background
- An affiliation with, or relating to large groups of people classed according to common racial, national, tribal, religious, linguistic or cultural origin or background
- Key to understanding an ethnic group is to at least be aware of the beliefs and traditions that are held to be true, especially as these relate to healthcare

**Culture**

- Customary beliefs, social forms and material traits of a racial, religious or social group
- Values, beliefs, practices and rules of a group
- Leininger (1995) suggests that culture is learned values, beliefs and pattered life ways that assist, support, facilitate or enable another individual or group to maintain health and well-being, to improve their human condition and life ways, or to deal with illness, handicaps or death
A Diverse American Population

Which person is Hispanic?
Additional Census Findings

• 1 in 4 Americans are of a race other than White
• 1/3 of American children are African American, Asian or Hispanic
• 1 in 10 citizens of the United States are foreign born
• 2010 census: “Race” and “Ethnicity” were different
  • Ethnic origin was considered to be a separate concept from race
  • People of Hispanic origin could belong to any racial category

Additional Census Findings: Hispanics

• 44.3 million Hispanics currently live in the United States
• Now the largest racial/ethnic group after Caucasians in the country
• From 2000-2006, Hispanics accounted for ½ of the nation’s growth rate
  • Hispanic growth rate (24.3%) was more than 3 times the growth rate of the total general population (6.1%)
Pharmacological Differences By Ethnicity/Race: “HEADLINERS”

Ethnic/Racial Drug Differences: African Americans

[Have been studied more than any other ethnic group in relation to differences in drug metabolism and response]

- *underlying hypertension prevalence is among the highest in the world…*

- *hypertension occurs at an earlier age than in other races…*

- *require a high dosage of angiotensin-converting enzyme (ACE) inhibitors or combined therapy with low-dose diuretics to effectively reduce blood pressure…*

(Chobanian et al., 2003; Wynne et al., 2007)
Ethnic/Racial Drug Differences: 
African Americans

• ...show less effective monotherapy with beta blocker and ACE inhibitors than Caucasians…

• African American Heart Failure Trial (A-HeFT) demonstrates that by adding isosorbide dinitrate (Isochron) and hydralazine (Apresoline) to standard therapy for heart failure increases survival in black patients with advanced failure

• The United States Food and Drug Administration approves the first drug, BiDil, especially labeled for use by African Americans…

• …require a higher dose of glucocorticoids than Caucasians to control their asthma symptoms, regardless of asthma status or severity

(Allseetter, 2005; Amudha 2003; Belle, 2006; Burchard, 2006; Matthews, 1995; Taniguchi, 1999; Taylor, 2004; Taylor, 2005)

Ethnic/Racial Drug Differences: 
Asians

• …a lower threshold of antipsychotic medications than Caucasians for both therapeutic and adverse events…

• ...need lower doses of lithium and antipsychotic medications…

• ...need lower doses of anxiolytics than Caucasians...

• ...cholesterol-lowering drug, Crestor, relabeled to urge doctors to lower the starting dose of the medicine for Asian patients to decrease their risk of muscle damage…

(Burchard, 2006; Burroughs, 2002; ISFM, 2003; Levy & Polatsek, 2002; Matthews, 1995; Pavlovich-Dains, 1999)
Ethnic/Racial Drug Differences: Hispanics

• ...Puerto Ricans have poorer responses to the asthma control drug, Itratropium bromide (Atrovent) ...

• ...may require lower doses of antidepressants than Caucasians ...

• ...Mexicans are better metabolizers of medications that utilize the CYP 450 2C19 subgroup of liver enzymes when compared to Caucasian and Asian counterparts ...

• ...require lower dosages of medications metabolized by the CYP 450 subgroup of enzymes ...

(Burchard et al., 2004; 2006; Burroughs, 2002; Lin & Poland, 2000; Luo et al., 2006; Pavlovich-Denis, 1999; Weisling, 2008)

Ethnic/Racial Drug Differences: Caucasians

• ...Whites benefit more than blacks when prescribed ACE inhibitors ...

Ethnic/Racial Drug Differences All Patients

• ...an analysis of a study involving 33,000 patients concludes that low-cost diuretics should be the first-step in hypertension treatment for patients of all races ...
Why do ethnic/racial drug differences exist?

Factors Contributing to Variability in Drug Response

**BIOLOGICAL FACTORS**
- Age
- Gender
- Genetics
- Disease

**CULTURAL FACTORS**
- Attitude
- Beliefs
- Family influence

**ENVIRONMENTAL FACTORS**
- Climate
- Parasites
- Pollutants
- Smoking
- Alcohol
- Drugs

**VARIABILITY IN:**
- Drug metabolism
- Drug receptors
- Drug response proteins
- Disease progression proteins
Ethnopharmacologic Drug Differences

• The major determinants of variations in drug response are a result of genetic factors.

• Genetic factors may result in ethnic/racial differences in:
  1. Drug metabolism
  2. Clinical response to medications
  3. Side effects of medications

Important Principles of Pharmacology: A Quick Review
Pharmacodynamics

• Physiologic responses to medications

• The study of the pharmacologic effect resulting from the interaction between the drug and the biologic system

• How drugs interact with cells, tissues and organs
  • Same for every human!

Pharmacodynamics

• Pharmacologic response to a drug may be mediated through:
  • A direct effect (binding with a specific receptor)
  OR
  • An indirect effect (inhibiting an enzyme in a protein synthesis pathway)

• The effects of a drug on the body
Pharmacokinetics

- Mechanism of action at the target site
- Study and analysis of the time course of the drug in the body
- The art of absorption, metabolism, distribution and elimination
- How the body interacts with drugs
  - Not the same in every human!

Pharmacogenetics and Pharmacogenomics
Pharmacogenetics/Pharmacogenomics

Pharmacogenetics:
- The study of single-gene genetic variations in drug response
- Drug response inherited differences in drug metabolism

Pharmacogenomics:
- The study of genetic variations in drug response of all genes

Genetics: Revisited

(From the Human Genome Project)
- Humans are 99.9% genetically similar among all races!
- Humans are also ~ 98% genetically similar to chimpanzees!
- That 0.1% may account for causing:
  - Variations of gene patterns among different races of humans
  - Individuals to react differently to medications
Genetics: Revisited

Genotype:
• An individual's genetic makeup

Phenotype:
• An individual's physical appearance or function as a result of interaction between the genotype and one's environment

Polymorphisms:
• Variations in gene structure that occur naturally in more than 1% of the population which may change a drug's action by changing its pharmacokinetics or pharmacodynamics

Genetics: Revisited

• Most common mechanism by which genetic differences modify drug responses: Altered drug metabolism
• Genetic ability to produce certain enzymes vary by race and ethnicity
• Variants are called SNP single nucleotide polymorphisms (SNIPs)

• Variability of the genome accounts for nearly all of the phenotypic differences seen in different individuals
• *Since different pathways can metabolically clear various drugs within the same class, ethnic differences may differ among a given ethnicity within the same drug class

(Burroughs, 2002; Kellner & Folks, 2001; Lehne, 2004; Levy & Polatsek, 2002; Munoz & Hilgenberg, 2005; Wynne et al., 2007)
Genetics: Revisited

- Most differences between people occur because of the different ways drugs are metabolized.
- Most drug metabolism genetic differences are monogenetic (one gene) genetic polymorphisms.
- Most drug metabolism takes place in the liver.
- Two major forms of metabolism:
  - Phase 1: oxidation, reduction and hydrolysis reactions.
  - Phase 2: conjugation reactions.

The CYP 450 System
**Cytochrome P450 (CPY450)**

- Major drug metabolizing enzyme system
- Comprised of multiple proteins
- Core of the system (active site) is a heme protein
- Requires molecular oxygen
- Largest amount of enzymes are located in the liver (#1), gut wall, and to a lesser degree in almost all body tissues (lungs, kidney, brain, skin, etc.)

*(Agins, 2008; Chen, 2006; Wynne et al., 2007)*

**Drug Metabolism Mediated by CYP 450**

**Major Subfamilies:**

1. CYP 3A4 (~ 50%)
2. CYP 2D6 (~ 25-30%)
3. CYP 2C9, CYP 2C10, CYP 2C19 (~ 15%)
4. CYP 1A2, CYP 2E1 + others (remaining ~ 15%)

*(Agins, 2008; Johnson, 1997; Morrison & Levy, 2004)*
CYP 450

- Characterizing interactions of the CYP 450 system is complex
- Race, gender, age, nutrition, stress and environmental factors may alter gene expression of individual families and subfamilies of CYP 450
- Individuals have different concentrations of CYP 450 enzymes in their liver and GI tract and therefore, different patients have different changes in isoenzyme activity
  - Children vs. elderly
  - Men vs. women
  - Smokers, alcoholics, malnourished, etc.

Premises of CYP 450

- Potential drug-drug interactions are predicted by substrates, inhibitors and inducers for each CYP 450 sub-family
- **Substrate**: given medication
- **Inducer**: stimulates the synthesis of CYP 450
  - Increases the rate of drug metabolism
  - Lowers the serum drug level
- **Inhibitor**: blocks the effects of CYP 450
  - Increases the level of another drug by competing for the same enzyme → toxicity
CYP Inducers

- Stimulate the synthesis of CY P450
- Increase the rate of drug metabolism
- Lower the serum drug level

CYP 3A4 Potential Interactions: Leading To SUB-therapeutic Drug Levels

<table>
<thead>
<tr>
<th>SUBSTRATES:</th>
<th>INDUCERS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>CCBs</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>Carbamezepine</td>
</tr>
<tr>
<td>Some statins (A, L, S) [Atorvastatin (Lipitor), Lovastatin (Mevacor), Simvastatin (Zocor)]</td>
<td>Pioglitazone</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>St. John’s Wort</td>
</tr>
<tr>
<td>PDE-5 inhibitors</td>
<td></td>
</tr>
<tr>
<td>Urge incontinence medications</td>
<td>*Substrates clear twice as fast when if a patient is taking an inducer!</td>
</tr>
<tr>
<td>Warfarin-R</td>
<td></td>
</tr>
</tbody>
</table>
CYP 1A2 Potential Interactions: Leading To SUB-therapeutic Drug Levels

<table>
<thead>
<tr>
<th>SUBSTRATES:</th>
<th>INDUCERS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Olanzapine (30%)</td>
<td>Tegretol</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Cigarette smoke</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Char-broiled meats</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Broccoli, cauliflower, cabbage</td>
</tr>
<tr>
<td>Caffeine</td>
<td></td>
</tr>
<tr>
<td>Warfarin-R</td>
<td>*Substrates clear twice as fast when if a patient is on an inducer!</td>
</tr>
</tbody>
</table>

(Clozing, 2008; Lehne, 2004; Wynne et al., 2007)

CYP Inhibitors

• Block the effects of CYP 450
• Increase the level of another drug by competing for the same enzyme → toxicity
# CYP 3A4 INHIBITION:
## Leading To Potential TOXIC Drug Levels

<table>
<thead>
<tr>
<th>SUBSTRATES:</th>
<th>INHIBITORS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>CCBs</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Some statins (A, L, S) [Atorvastatin (Lipitor), Lovastatin (Mevacor), Simvastatin (Zocor)]</td>
<td>Itraconazole (Sporonox)</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>PDE-5 inhibitors</td>
<td>Protease inhibitors</td>
</tr>
<tr>
<td>Warfarin-R</td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td>Fentanyl; Methadone</td>
<td></td>
</tr>
<tr>
<td>Plavix</td>
<td>*Statin + Clarithromycin = increased toxic effects!</td>
</tr>
<tr>
<td></td>
<td>*Viagra + Grapefruit juice = prolonged erection!</td>
</tr>
</tbody>
</table>

(Atkins, 2008; Lehne, 2004; Wynne et al., 2007)

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# CYP 2D6 INHIBITION:
## Leading To Potential TOXIC Drug Levels

<table>
<thead>
<tr>
<th>SUBSTRATES:</th>
<th>INHIBITORS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomoxetine (Strattera)</td>
<td>Paxil</td>
</tr>
<tr>
<td>Tricyclic Antidepressants</td>
<td>Prozac</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics: Haloperidol (Haldol), Perpheadine (Trilafon), Risperidone (Risperdal)</td>
<td></td>
</tr>
<tr>
<td>Beta blockers: Metoprolol (Lopressor), Propranolol (Inderal)</td>
<td></td>
</tr>
<tr>
<td>Narcotics: Codeine, Oxycodone, Morphine</td>
<td></td>
</tr>
</tbody>
</table>

(Atkins, 2008; Lehne, 2004; Wynne et al., 2007)
### CYP 2C9 INHIBITION:
Leading To Potential TOXIC Drug Levels

<table>
<thead>
<tr>
<th>SUBSTRATES:</th>
<th>INHIBITORS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Warfarin – S</td>
<td>Fluconazole</td>
</tr>
<tr>
<td>Losartan, Valsartan</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Glipizide, Glyburide</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Rosiglitizone</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td></td>
</tr>
</tbody>
</table>

(Agins, 2008; Lehne, 2004; Wynne et al., 2007)

### CYP 2C19 INHIBITION:
Leading To Potential TOXIC Drug Levels

<table>
<thead>
<tr>
<th>SUBSTRATES:</th>
<th>INHIBITORS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Warfarin – S</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Lansoprazole</td>
</tr>
<tr>
<td>Diazepam</td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
</tr>
</tbody>
</table>

(Agins, 2008; Lehne, 2004; Wynne et al., 2007)
### CYP 1A2 INHIBITION:
Leading To Potential TOXIC Drug Levels

<table>
<thead>
<tr>
<th>SUBSTRATES:</th>
<th>INHIBITORS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Quinolone antibiotics: Especially Ciprofloxacin</td>
</tr>
<tr>
<td>Olanzapine (30%)</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Imipramine</td>
<td></td>
</tr>
<tr>
<td>Mexillitene</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
</tr>
<tr>
<td>Caffeine</td>
<td></td>
</tr>
<tr>
<td>Ramelteon</td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td></td>
</tr>
<tr>
<td>Warfarin-R</td>
<td><em>If on an inhibitor (e.g., Fluoroquinolone), caffeine cannot clear from the body!</em></td>
</tr>
</tbody>
</table>

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### Pharmacogenetics

- Regarding CYP 450 metabolism, of course, not all individuals are the same
- Genetic polymorphisms exist for many drugs
- A comprehensive family drug history is very important in the interview of the patient!

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Ethnic/Racial Factors Affecting Drug Metabolism: Genetics

Genetically Polymorphic CYP 450 Enzymes

- **CYP 2D6**
  - ~25-30% CYP 450 drug metabolism
- **CYP 2C9 & CYP 2C19**
  - ~15% CYP 450 drug metabolism

**CYP 2D6**

- Geographic (racial) differences in gene duplication
- 104-fold variation in rates (e.g., metabolism)
- Hypothesized to have arisen 5,000-10,000 years ago due to dietary selection of alleles carrying multiple active CYP/2D6 gene copies in North East African populations

(Agins, 2008; Lehne, 2004; Wynne et al., 2007)
CYP 2D6 Polymorphisms

Four Types of Metabolizers:

- **Poor Metabolizers (PMs)**
  - Inherit two deficient CYP 2D6 alleles = metabolize drugs slower
  - Leads to high levels of unmetabolized drug = potential for drug-drug interactions and adverse events

- **Intermediate Metabolizers (IMs)**
  - High spectrum of metabolic activity; ranges from better than that of the PMs to close to that of EMs

- **Extensive Metabolizers (EMs)**
  - Normal or reduced CYP 2D6 function
  - Expressed by the majority of the population = normal

- **Ultrarapid Metabolizers (UEMs)**
  - Greater than normal CYP 2D6 function: multiple copies of the CYP 2D6 gene expressed
  - May lead to loss of therapeutic efficacy at normal doses

CYP 2D6: Effects of Phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Drug Metabolism Effects</th>
<th>Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Metabolizers (PMs)</td>
<td>Slowed</td>
<td>• Greater potential for drug-drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Drug conversion to active metabolites is slower; potential lower efficacy</td>
</tr>
<tr>
<td>Ultrarapid Metabolizers (UMs)</td>
<td>Accelerated</td>
<td>• Drug is eliminated faster</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Potential for lower efficacy</td>
</tr>
</tbody>
</table>

(Bernard et al., 2006)
Which ethnicities/races are most at risk for adverse events or drug-drug interactions from CYP 2D6 polymorphisms?

<table>
<thead>
<tr>
<th>Population</th>
<th>PM phenotype (%)</th>
<th>Diminished activity of IMs (%)</th>
<th>UM phenotype (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td></td>
<td></td>
<td></td>
<td>[1]</td>
</tr>
<tr>
<td>American</td>
<td>7.7</td>
<td>4.3</td>
<td>[20,40]</td>
<td></td>
</tr>
<tr>
<td>British</td>
<td>8.9</td>
<td></td>
<td>[26]</td>
<td></td>
</tr>
<tr>
<td>Polish</td>
<td>8.3</td>
<td></td>
<td>[73]</td>
<td></td>
</tr>
<tr>
<td>Swiss</td>
<td>10</td>
<td></td>
<td>[23]</td>
<td></td>
</tr>
<tr>
<td>Danish</td>
<td></td>
<td>0.8</td>
<td>[22]</td>
<td></td>
</tr>
<tr>
<td>German</td>
<td>7.7</td>
<td>0.8</td>
<td>[49]</td>
<td></td>
</tr>
<tr>
<td>Swedish</td>
<td></td>
<td>1</td>
<td>[59]</td>
<td></td>
</tr>
<tr>
<td>Spanish</td>
<td></td>
<td>0.8</td>
<td>[23]</td>
<td></td>
</tr>
<tr>
<td>Turkish</td>
<td>1.5</td>
<td>8.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canadian</td>
<td>3.0</td>
<td>4.0</td>
<td>[74]</td>
<td></td>
</tr>
<tr>
<td>African</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>1.9–7.3</td>
<td>4.9</td>
<td>[20,30–42]</td>
<td></td>
</tr>
<tr>
<td>Nigerian</td>
<td>0–8.1</td>
<td></td>
<td>[35,30]</td>
<td></td>
</tr>
<tr>
<td>Ghanaian</td>
<td>6.0</td>
<td></td>
<td>[37]</td>
<td></td>
</tr>
<tr>
<td>Ethiopian</td>
<td>1.8</td>
<td>29</td>
<td>[23]</td>
<td></td>
</tr>
<tr>
<td>South African</td>
<td>19</td>
<td></td>
<td></td>
<td>[38]</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>51</td>
<td></td>
<td>[1]</td>
</tr>
<tr>
<td>Japanese</td>
<td>0</td>
<td></td>
<td>[29]</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>&lt;1.0</td>
<td>0.9</td>
<td>[26,75]</td>
<td></td>
</tr>
<tr>
<td>Thai</td>
<td>1.2</td>
<td></td>
<td>[27]</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>1.8–4.8</td>
<td></td>
<td>[30–33]</td>
<td></td>
</tr>
<tr>
<td>Saudi Arabian</td>
<td>1–2</td>
<td>3–9</td>
<td>21.0</td>
<td>[1,51,76]</td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colombian</td>
<td>6.6</td>
<td>1.7</td>
<td>[47]</td>
<td></td>
</tr>
<tr>
<td>Mexican</td>
<td>3.2</td>
<td></td>
<td>[46]</td>
<td></td>
</tr>
<tr>
<td>Panamanian/Ancestral</td>
<td>2.2–4.4</td>
<td></td>
<td></td>
<td>[45]</td>
</tr>
<tr>
<td>Nicaraguan</td>
<td>3.6</td>
<td></td>
<td></td>
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Note: IM = intermediate metabolizer; PM = poor metabolizer; UM = ultrarapid metabolizer.
**Ethnic/Racial Frequency of Poor Metabolizers (PMs) of CYP 2D6**

- **Whites**: ~7-10%
- **Africans**: ~1-19%
- **Asians**: ~0-2%
- **Hispanics**: ~2.2-6.6%

*PMs have a greater potential for drug-drug interactions and adverse events (toxicity).*

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**Common Drugs Metabolized by CYP 2D6: Clinical Implications**

### Antidepressants
- TCAs
- Venlafaxine (Effexor)
- Fluoxetine (Prozac)
- Paroxetine (Paxil)

### Antipsychotics
- Haloperidol (Haldol)
- Perphenazine (Trilafon)
- Risperidone (Risperdal)

### Dextromethorphan

### Atomoxetine

### Duloxetine

---

**Beta Blockers**
- Metoprolol (Lopressor)
- Propranolol (Inderal)
- Timolol (Blocadren)

**Narcotics**
- Codeine
- Oxycodone
- Morphine
- Tramadol (Ultram)

*(Agins, 2008; Lehne, 2004; Wynne et al., 2007)*
Ethnic/Racial Frequency of Ultrarapid Metabolizers (UMs) of CYP 2D6

Whites ~ 0.8-10%
    (American: ~ 4.3%)

Africans ~ 4.9-29%
    (American: 4.9%; Ethiopian 29%)

Asians ~ 0-21%
    (All except Saudi Arabian < 1%;
     Saudi Arabian: 21%)

Hispanics ~ 1.7%

*UMs metabolize drugs very quickly, so dosages may need to be INCREASED for therapeutic clinical effects.

CYP 2C9

• 1-3 % of Caucasians are Poor Metabolizers (PMs) with no CYP 2C9 function

• May affect the clearance of:
  • Phenytoin
  • Warfarin-S
  • Losartan
  • Valsartan
  • Glipizide
  • Glyburide
  • Rosiglitizone
  • NSAIDs
  • Celecoxib
  • Rosuvastatin

Clinical Example:
• A patient may need a very low dose of Coumadin because it cannot be cleared effectively by the body
CYP 2C19

- Poor Metabolizers (PMs) with no CYP 2C19 function
- May affect the clearance of:
  - Amitriptyline
  - Clomipramine
  - Phenytoin
  - Progesterone
  - Propranolol
  - PPIs
    - Lansoprazole
    - Omeprazole
    - Pantoprazole
    - Rabeprazole
    - Warfarin

Caucasians: 3 – 5%
Asians: 15-20%

Multifactorial Contributors to Ethnic/Racial Differences in CYP 450 Metabolism

- Diet
- Lifestyle
- Environment

CYP 450 enzymes can be induced or inhibited by:
- Alcohol
- Tobacco constituents
- Caffeine
- Certain vegetables
- Char-broiled foods
- Grapefruit juice
- Pollutants: Air & Water
Clinical Implications

1. CYP 450 polymorphisms are more likely to increase in the future as a result of:
   - Polypharmacy
   - Use of over-the-counter medications
   - Use of herbal preparations and home remedies
   - Continued multiethnic immigration into the United States

2. More adverse drug-drug reactions (especially toxicity) will likely occur

3. Advances in genotyping are under way as new tests become available

4. All potential contributing factors to drug polymorphisms will require more heightened monitoring by nurses and advance practice clinicians

Genotype Testing
Do any ethnic/racial drug differences exist specifically related to urology?

Commonly Prescribed Drugs: Urology

**Antibiotic Agents:**
- Ciprofloxacin (Cipro)
- Clarithromycin (Biaxin)
- Levofoxacin (Levaquin)
- Nitrofurantoin (Macrobid)
- Metronidazole (Flagyl)
- Trimethoprim-sulfamethoxazole (Bactrim)

**Antifungal Agents:**
- Fluconazole (Diflucan)
- Ketoconazole (Nizoral)

**Alpha-adrenergic Blockers:**
- Doxazosin (Cardura)
- Tamsulosin (Flomax)
- Prazosin (Minipress)
- Terazosin (Hytrin)

**PDE-5 Inhibitors:**
- Sildenafil (Viagra)
- Tadalafil (Cialis)
- Vardenafil (Levitra)

**5-alpha Reductase Inhibitors:**
- Dutasteride (Avodart)
- Finasteride (Proscar)

**Muscarinic Receptor Antagonists:**
- Tolterodine (Detrol)
- Solifenacin (Vesicare)
- Oxybutynin ( Ditropan, Oxytrol)
- Flavoxate (Urispas)
- Darifenacin (Enablex)
Which urology medications have been tested for drug differences in ethnicity/race?

Urology Medications Tested For Drug Differences In Ethnicity/Race

**Antibiotic Agents:**
- Ciprofloxacin (Cipro)
- Clarithromycin (Biaxin)
- Levofoxacin (Levaquin)
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Urology Medications Tested
For Drug Differences In Ethnicity/Race

**Antibiotic Agents:**
- Ciprofloxacin (Cipro) – N/I
- Clarithromycin (Biaxin) – N/I
- Levofoxacin (Levaquin) – NO
- Nitrofurantoin (Macrobid) – N/I
- Metronidazole (Flagyl) – N/I
- Trimethoprim-sulfamethoxazole (Bactrim) – N/I

**Antifungal Agents:**
- Fluconazole (Diflucan) – N/I
- Ketoconazole (Nizoral) – N/I

**Alpha-adrenergic Blockers:**
- Doxazosin (Cardura) – N/I
- Tamsulosin (Flomax) – N/I
- Prazosin (Minipress) – N/I
- Terazosin (Hytrin) – N/I

**PDE-5 Inhibitors:**
- Sildenafil (Viagra) – N/I
- Tadalafil (Cialis) – N/I
- Vardenafil (Levitra) – N/I

**5-alpha Reductase Inhibitors:**
- Dutasteride (Avodart) – N/S
- Finasteride (Proscar) – N/S

**Muscarinic Receptor Antagonists:**
- Tolterodine (Detrol) – NO
- Solifenacin (Vesicare) – N/C
- Oxybutynin ( Ditropan, Oxytrol) – N/I
- Flavoxate (Urispas) – N/I
- Darifenacin (Enablex) – N/C

N/I: No Information     N/S: Not Studied     N/C: No Conclusions
NO: No Ethnic/Racial Differences

Which urology drugs are potentially most likely to be involved in adverse drug-drug interactions regardless of ethnicity/race?
Urology Potential Adverse Drug Events:
Regardless of Ethnicity/Race

**Antibiotic Agents:**
- Ciprofloxacin (Cipro)
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Which urology drugs are most likely to have different effects from one ethnicity/race to another?

### Urology Adverse Drug Events:
**Potential Different Effects from One Ethnicity/Race to Another**

**Antibiotic Agents:**
- Ciprofloxacin (Cipro)
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- Levofoxacin (Levaquin)
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Other Considerations for Nurse Practitioners
FDA: Med Watch

www.fda.gov/medwatch

Main Goals:
1. Increase awareness of medical product (drug) induced disease and the importance of reporting
2. Clarify what should and should not be reported
3. Facilitate the ease of reporting
4. Provide feedback to health professionals about new safety issues

Special Considerations When Monitoring Drug Therapy In Multiethnic Populations
Special Considerations When Monitoring Drug Therapy In Multiethnic Populations

**Increasing Cultural Competence**
- Culture
- Socioeconomics
- Values
- Beliefs
- Rituals

- Religion
- Symbolization
- Compliance
- Adherence
- Others

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Special Considerations When Monitoring Drug Therapy In Multiethnic Populations: African Americans

- African Americans may discontinue medications once symptoms subside, often doubting the need for further therapy
- Touch is viewed as an essential part of healthcare – personal space may be minimal
- Heavily rely on religious rituals and a minister's advice
- Health viewed as a gift from God
  - Illness and suffering may be God's will or evil influences

(Burroughs, 2002; ISFM, 2003; Levy & Polatsek, 2002; Pavloitch-Denis, 1999; Wynne et al., 2007; Zweber, 2002)
Special Considerations When Monitoring Drug Therapy In Multiethnic Populations: African Americans

- Folk healers and folk medicine may be common
  - Cod liver oil to prevent colds
  - Copper or silver bracelets to protect from harm
- Allopathic healthcare often not a priority for prevention
- May believe in voodoo (especially Haitians and Africans)

Special Considerations When Monitoring Drug Therapy In Multiethnic Populations: Hispanics

- Believe it is unnecessary to continue pharmacotherapy once symptoms abate
  - Especially problematic for diabetics where ongoing medication is required
- Often esteem the mother or grandmother, especially of the husband, as the primary decision-maker of health related issues
- Balance of “hot and cold” are essential
  - “Hot/cold” illnesses and medications
  - “Wet/dry” concepts
  - Illness is treated with the opposite type medicine: hot for cold, and cold for hot
    - May not take PCN for a “hot” illness because PCN is viewed as a “hot” medicine
Special Considerations When Monitoring Drug Therapy In Multiethnic Populations: Hispanics

- Illness may be caused by malojo (evil eye)
  - Healthcare workers can inadvertently give this look
- Strong religious association
  - Health is a gift from God and reward for good behavior
- Illness prevention strategies: eating proper foods, working the proper amount of time, wearing religious medals and sleeping with relics
- Curanderas may be common
  - Treat with a variety of herbs, teas, visits to shrines, medals, candles and promises to God to change behavior

(Andrade-Cetto & Heinrich, 2005; ISFM, 2003; Levy & Polatsek, 2002; Burroughs, 2002; Pavlovich-Danis, 1999)

Special Considerations When Monitoring Drug Therapy In Multiethnic Populations: Hispanics

- Often concerned about the potential for addiction when taking medication for prolonged periods of time
- Often expect injections as a necessary component of effective treatment for disease
  - Taking oral medications may be viewed as less effective treatment

(Andrade-Cetto & Heinrich, 2005; ISFM, 2003; Levy & Polatsek, 2002; Burroughs, 2002; Pavlovich-Danis, 1999)
Special Considerations When Monitoring Drug Therapy In Multiethnic Populations: Asians

• Vast array of herbal remedies are used: potential for drug-drug interactions

• Eye contact may be a sign of disrespect

• Using the word, “yes” is common which simply means, “I’m being polite” (and maybe, understanding what is being said)

• Esteem elders’ views, wishes and “authority,” among other members of the family

• Diabetes is relatively less common in Asians
  ∗ Dietary requirements may be difficult to follow, especially considering their way of thinking in regard to food

Special Considerations When Monitoring Drug Therapy In Multiethnic Populations: Asians

• Well insured in comparison to other races
  ∗ (18% of U.S. Asians uninsured) – lowest of all minority groups

• Only ~ ½ of Asians over the age of 65 make as many visits to healthcare providers as Whites

• Longer life expectancies and lower death rates from all causes than the general population

• Many influenced by Shinto, a religious orientation
  ∗ Evil is caused by outside spirits (pleasing good spirits is important to health)
Special Considerations When Monitoring Drug Therapy In Multiethnic Populations: Asians

Japanese:
- Japanese (and other Asian) females may be open to talking with a female healthcare provider, but not a male
- Japanese esteem drug safety more than effectiveness
  - May explain the usual belief and practice
  - of using lower doses of medication and resultant fewer reported side effects

Chinese:
- Health is a result of forces that rule the world: yin (cold) and yang (hot)
  - Cold illnesses (diarrhea) are treated with hot herbs and food; hot illnesses (HTN) are treated with cold herbs and foods
  - Illness may be diagnosed by pulses and color/texture of the tongue

Special Considerations When Monitoring Drug Therapy In Multiethnic Populations: Asians

Filipinos:
- Subscribe to yin and yang
- God’s will and supernatural forces determine illness
  - Illness is punishment for violations of God’s will
  - Amulets and religious medals may be worn as a shield from witchcraft or as a good-luck charm
Special Considerations When Monitoring Drug Therapy In Multiethnic Populations: Caucasians

• Generally viewed as intolerant to pain, while other cultures accept pain as a part of life
• Perceive eye contact as communicating interest and honesty
• Most hold high expectations that disease will be cured and/or managed through powerful medications
• Strong family ties: males are viewed as the dominant force/decision-maker

(Burroughs, 2002; ISFM, 2003; Levy et al., 2002; Pavlovich-Danis, 1999; Zweber, 2002)

Special Considerations When Monitoring Drug Therapy In Multiethnic Populations: Caucasians

• Strong religious ties
  • Religious medals and rituals often used to prevent illness and heal
• Increasing number using:
  • Alternative sources of healthcare
  • Herbal therapies
• Most both believe and expect that a prescription is a necessary component when seeking care in the doctor’s or practitioner’s office

(Burroughs, 2002; ISFM, 2003; Levy et al., 2002; Pavlovich-Danis, 1999; Zweber, 2002)
Final Thoughts

- Race is an imprecise label for potential variations in genetics
  - Prudent to consider ethnicity/race similarly to age, sex, lifestyle, culture, etc.
- Toward future individualized drug treatment, the clear identification of medications most likely to cause adverse effects, coupled with the clinician’s knowledge of pharmacokinetics, may greatly decrease risk for many vulnerable patients

Summary Points

1. The premises that govern drug interactions occurring in various ethnicities/races are complex, multifactorial and often difficulty to predict.

2. Drug-drug interactions are well documented and will continue to occur, regardless of one’s ethnicity or race.

3. Race is an inadequate indicator of genetic variations between individuals.

4. Patients at greatest risk for adverse drug reactions can now be identified through genetic testing.
Summary Points

5. The incidence of drug-drug reactions will likely increase in the future considering the vast immigration of people into the United States from other countries and mixing of genetic pools.

6. It is important to consider major cultural scripts and potential underpinning beliefs affecting healthcare decision-making in various ethnic/rational groups.

7. Nurses and advance practice clinicians are at the forefront for recognizing those at greatest risk for adverse drug events.

8. Future patient safety, in large part, depends on nurses’ heightened awareness, understanding and clinical application of pharmacogenetics and pharmacogenomics.

THE END