

Ethnopharmacology

Understanding How Ethnicity Can Affect Drug Response Is Essential to Providing Culturally Competent Care

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Ethnopharmacologic research has revealed that ethnicity significantly affects drug response. Genetic or cultural factors, or both, may influence a given drug's pharmacokinetics (its absorption, metabolism, distribution, and elimination) and pharmacodynamics (its mechanism of action and effects at the target site), as well as patient adherence and education. In addition, the tremendous variation within each of the broader racial and ethnic categories defined by the U.S. Census Bureau (categories often used by researchers) must be considered. Nurses need to become knowledgeable about drugs that are likely to elicit varied responses in people with different ethnic backgrounds, as well as the potential for adverse effects. The existing ethnopharmacologic research focuses primarily on psychotropic and antihypertensive agents, as does this article. Cultural assessment of every patient is vital; thus Leininger's Sunrise Model and Giger and Davidhizar's Transcultural Assessment Models are briefly described as well. *Holist Nurs Pract* 2006;20(5):227–234

The relatively new field of ethnopharmacology is hampered by a lack of clarity caused, in part, by the fact that some researchers use the words race, ethnicity, and culture synonymously, even though they have quite distinct meanings. For example, the term Hispanic can refer to Puerto Ricans, Mexicans, Peruvians, and Chileans, among many others, and describes more than 38 million Americans.¹ But some researchers have used the term to denote a racial category, despite the fact that Hispanics can be of any race. Such imprecision has raised quite valid questions about the accuracy of some data.

This imprecision also reflects a scientific uncertainty: it's impossible to know a person's genotype simply by looking at her, or the degree to which environment affects someone's genes merely by

knowing his nationality. Nurses have made significant efforts to clear the confusion, but an important question remains: how is a “culturally competent” nurse to understand the ways in which drug response is affected by ethnicity—that amalgam of genetic and cultural influences that makes up a human life?

As the U.S. population becomes more diverse ethnically, such questions have become more pressing. Cultural competence, defined as the process of learning to “work within the cultural context” of the patient,² involves knowledge not only of patients' beliefs and values about health and illness, but also of their responses to treatment, including drug therapies. Ethnopharmacology is the study of the effect of ethnicity on responses to prescribed medication, especially drug absorption, metabolism, distribution, and excretion. The field incorporates pharmacogenetics, the study of genetic variations in responses to drugs.

The value of cultural competence has been well documented, and the need for it is becoming increasingly urgent. In 2000, according to the U.S. Census Bureau, the national population stood at about 281,422,000; of this total, 12.5% self-identified as Hispanic or Latino; 12.3%, as black or African American; 3.6%, as Asian; and almost 1% as American Indian or Alaskan native.³ The most recent data show that some population groups are continuing

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This article was previously published in *AJN*, Volume 105, Issue 8, pp. 40–48 (2005).

Muñoz discloses that she received an honorarium and expenses for participating in an invitational session for physicians, pharmacists, and psychiatric nurses held in Miami, Fla, and sponsored by AstraZeneca, which manufactures Inderal, a drug mentioned in this article. The authors of this article have no other significant ties, financial or otherwise, to any company that might have an interest in the publication of this educational activity.

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to grow much faster than others. For example, between April 2000 and July 2003, the growth rates for Hispanic and Asian Americans were reported to be 13% and 12.5%, respectively, compared with a growth rate of 3.3% for the total population.⁴

Although sometimes used interchangeably, the terms race, culture, and ethnicity have distinct meanings. Dorland's Illustrated Medical Dictionary defines race as "a class of persons of a common lineage; in genetics, races are considered as populations having different distributions of gene frequencies"; the term generally reflects the geographic origins of ancestry. Although the usefulness of the classification has been debated, given the ambiguity of even self-defined racial identity,^{5,6} the term remains widely used in clinical research. Leininger has described culture as an integrated system of learned beliefs, values, and customs common to a particular group of people; typically these are passed down from generation to generation.⁷ Ethnicity can refer to shared cultural bonds, a common genetic heritage, or both.

Although varied responses to other treatment modalities no doubt exist, this article focuses on similarities and differences in how people from various ethnic groups respond to prescribed medications. (Interactions that may occur between prescribed drugs and herbal or "folk" remedies are beyond the scope of this article.)

VARIATIONS IN DRUG RESPONSES

Studying how ethnicity affects drug response is challenging, in part because of the tremendous variations that exist within each ethnic group. Many studies have used broad categories when classifying participants without differentiating among subgroups (for example, using the term "Asians" to refer to people of Korean, Chinese, Japanese, Indian, Pakistani, and Vietnamese ancestry, among others). Also, as Burchard and colleagues have observed, findings of ethnic differences can create more anxiety than they allay, given the United States' long history of prejudice and discrimination against racial and ethnic minorities.⁸ And some questions have been raised about the accuracy of data collected, partly because the definitions of race and ethnicity are not consistent.^{5,6}

Historically, most clinical drug trials have been conducted using white men; the results have then been generalized to all patients receiving the drugs studied.

As Dawkins and Potter point out, this has been the case even when the targeted disorder or illness is most prevalent in groups other than white men.⁹ Nevertheless, data have been accumulating that strongly suggest that ethnicity influences response to certain medications,^{10,11} a fact of which many clinicians remain largely unaware.

Within the last 15 years, ethnopharmacologic research has uncovered significant differences in how people in diverse ethnic groups metabolize certain drugs,¹⁰ with regard to both pharmacodynamics (a drug's mechanisms of action and its effects at the target site) and pharmacokinetics (the "movement" of drugs, referring to drug absorption, metabolism, distribution, and elimination).¹² Research has shown that genetic variations in certain enzymes may cause differing drug responses (although the precise mechanism is unknown); also, certain ethnic groups have more of these variations than others do. (See "Medication Selection by Genotype," May 2004.) Moreover, factors such as diet and tobacco use can influence a gene's expression, which can in turn alter a drug's effect.¹² Most ethnopharmacologic research to date has focused on drugs in two classes: psychotropic agents and antihypertensive agents. (One possible reason for the focus on antihypertensives may be the relatively high incidence of hypertension and cardiovascular disease in some minority populations. For example, according to the American Heart Association, the prevalence of high blood pressure among non-Hispanic blacks is almost 39%, compared with 27% among non-Hispanic whites.¹³)

Psychotropic agents

Most psychotropic drugs are metabolized in the liver in two phases, an oxidation phase (phase 1) and a conjugation phase (phase 2). One group of enzymes, the cytochrome P-450 (CYP) enzymes, has been the focus of much research because these enzymes are responsible for the phase 1 metabolism of many widely prescribed drugs, including most antipsychotics and antidepressants. There are many CYP enzyme subgroups; these are typically identified by letters and numbers (for example, CYP2). Many studies have indicated that genetic abnormalities in the CYP enzymes are not only extremely common but have profound implications for drug response.^{12,14,15} And as Keltner and Folks have noted, it appears that the "genetic ability to produce" these enzymes "will vary by race or ethnic group."¹⁶

For example, genetic changes in certain CYP enzymes, including CYP2D6, have been shown to affect the rate of drug metabolism, which in turn affects drug plasma levels at a given dosage. The CYP2D6 gene is “unique in that the gene is often duplicated or multiplied.”¹² People who have more than two functional copies of the CYP2D6 gene have faster than normal enzyme activity and are known as “ultrarapid metabolizers,” whereas those with two nonfunctional copies of the gene have slower than normal enzyme activity and are known as “poor metabolizers.”^{12,17} Ultrarapid metabolizers will metabolize a drug quickly, resulting in lower serum concentrations, whereas poor metabolizers metabolize the drug more slowly, resulting in higher serum levels at the same dosage. Luo and colleagues found that the frequency at which genetic abnormalities occur in these enzymes varied significantly among four ethnic groups: 18% of Ethiopian Jews and 13% of Sephardic Jews had more than two functional CYP2D6 genes and were predicted to be ultrarapid metabolizers; only 6% of Yemenite Jews and 4% of Bedouin Arabs shared the mutation.¹⁷ (Depending on which genes have abnormalities, a person can be an ultrarapid metabolizer of some drugs and a normal or poor metabolizer of others.)

In an important early study, Lin et al examined the effects of haloperidol in three groups of healthy volunteers, which they identified as “Caucasians,” “American-born Asian Americans,” and “foreign-born Asians.”¹⁸ (More details on the subjects’ nationalities were not reported.) When administered specified doses of haloperidol, both Asian groups had significantly higher serum concentrations of the drug than the white group did, even when body surface area was considered.

The same researchers then conducted a second study in Asian and white patients diagnosed with schizophrenia, administering haloperidol in fixed doses for two weeks and then in variable doses determined by clinical response for 10 weeks.¹⁸ They found that when haloperidol was given in variable doses, Asians required lower doses than whites did; when it was given at fixed doses, Asians showed significantly more extrapyramidal symptoms than whites given the same dose. A longitudinal study also determined that the dosage of haloperidol that provided the optimal response with minimal extrapyramidal symptoms was significantly lower for Asian patients than for whites.¹⁹

Differences in clinical responses also occur within ethnic groups. Researchers have tended to use broad

categories of race and ethnicity based on those used by the U.S. Census Bureau. (In 2000 these were white, black or African American, Asian, native Hawaiian and other Pacific Islander, and American Indian and Alaskan native; people who identify as Hispanic or Latino may be of any race.) But a tremendous number of subgroups exist, and studies have found marked differences in health status among them. For example, one recent study found significant differences in risk for hypertension among various Pakistani ethnic groups (Muhajir, Punjabi, Sindhi, Pashtun, and Baluchi), even after adjusting for sociodemographic and other major risk factors (response to pharmacotherapy was not included in the investigation).²⁰ Systematic investigation of variations in drug response among specific ethnic subgroups would lead to improved clinical understanding and thus better patient care.

Traditional antipsychotics include chlorpromazine (Thorazine), fluphenazine (Prolixin, Permitil), and haloperidol (Haldol). Research has suggested that Hispanics may require lower doses of antipsychotic medications than whites do. A retrospective study by Ruiz and colleagues examined data from a group of foreign-born Hispanic and Asian patients diagnosed with schizophrenia.²¹ The researchers converted dosages of traditional antipsychotic agents to “chlorpromazine equivalents,” and found that the Hispanic patients required lower dosages compared with a control group of “general” patients. (The researchers did not specify the antipsychotic agents; the general patient group was “drawn from a large multiethnic community.”) Another study of 398 outpatients receiving antipsychotic medications, including haloperidol, fluphenazine, chlorpromazine, and thioridazine (Mellaril), found that blacks were at greater risk for developing tardive dyskinesia than whites were.²² A literature review by Tran and colleagues supported this conclusion.²³

Newer, “atypical” antipsychotic agents such as risperidone (Risperdal), clozapine (Clozaril), and olanzapine (Zyprex, Zydys) have been subjected to limited ethnopharmacologic study. From anecdotal and research data available, Frackiewicz and colleagues reviewed the effects of both traditional and newer antipsychotics in Asians, Hispanics, blacks, and whites.²⁴ They determined that the newer medications “may be preferable in the treatment of ethnic minorities” because they caused fewer extrapyramidal and other adverse effects. In one study, Korean American and white patients were given therapeutic

doses of clozapine; their responses were subsequently measured using the Brief Psychiatric Rating Scale.²⁵ The Korean American group responded better than the white group did, even though they received lower doses and showed lower serum concentrations of the drug; however, the Korean Americans also had a higher incidence of anticholinergic and other adverse effects. And in reviewing the effectiveness of olanzapine, Tran and colleagues asserted that the drug “offers significant advantages over many existing antipsychotics” in black patients.²³ For example, olanzapine was associated with fewer involuntary movements in blacks than was haloperidol.

It should be noted that, in another review, Frackiewicz and colleagues cautioned that some findings suggest that the differences in drug responses in blacks (and other minority groups) “may be due to clinician biases and prescribing practices rather than to pharmacokinetic or pharmacodynamic variability.”²⁴ Others have made similar observations; future researchers should control for this possibility.

Tricyclic antidepressants

A literature review by Lawson found that blacks given tricyclics were likely to have faster therapeutic responses, have higher serum concentrations, and report more adverse effects than whites were.²⁶ A review by Strickland and colleagues reported similar findings.²⁷ For example, blacks appeared to have a greater risk of delirium caused by tricyclics than whites did.

Although the research in Hispanic populations has been limited and much of it was conducted in the 1980s, there is some evidence that adverse effects of tricyclics occur at much lower dosages in Hispanics than in whites. In a literature review, Mendoza and colleagues describe a retrospective study conducted in 1982 of Hispanic (primarily Puerto Rican) and “Anglo” women who were given tricyclics.²⁸ Dosages given the Hispanic women were half those given to Anglo women, yet comparable outcomes were achieved; however, the Hispanics reported adverse effects more often. Greater tissue sensitivity in Hispanics and Asians to tricyclics may explain why these populations achieve therapeutic responses to these drugs at lower dosages than those required for whites.²⁹

Newer antidepressants such as the selective serotonin reuptake inhibitors are now being widely prescribed, but as yet very few ethnopharmacologic studies have been conducted.

Lithium

There is evidence that blacks may require lower doses of lithium (Eskalith and others) than white patients do. In one study, Strickland and colleagues examined the effects of lithium in 12 black and 22 white patients with bipolar disorder.³⁰ All were in remission. Although patients in both groups received similar daily dosages, blacks reported more lethargy and dizziness than whites did. Plasma concentrations of the drug were similar in the two groups, but erythrocyte lithium concentrations were 60% higher in blacks than in whites.³⁰ And in 1980 Okpaku and colleagues found that serum lithium levels remained higher in healthy black volunteers than in healthy white volunteers 25 hours after receiving lithium, although the sample size ($N = 8$) was small.³¹ Given lithium’s narrow therapeutic range and the severity of symptoms of lithium toxicity, research is needed to examine the risk of toxicity in populations that demonstrate lithium sensitivity.

Antihypertensive drugs

The role of CYP enzymes in the metabolism of antihypertensives is not yet well understood. But ethnic variation in drug response has been demonstrated for many such agents, according to a review by Burroughs and colleagues in 2002.¹⁰ For example, captopril (Capoten), an angiotensin-converting enzyme (ACE) inhibitor, has reportedly been found to be less effective in blacks than in whites.³² The effectiveness of another ACE inhibitor, enalapril, was evaluated in white and black patients with left ventricular dysfunction.³³ The patients, who self-identified as white ($n = 1,196$) or black ($n = 800$), were matched for important variables such as age, sex, and left ventricular ejection fraction and then randomly assigned to receive enalapril or placebo. At one year, the white patients showed significant reductions in blood pressure, and the black patients did not; the black patients also had higher rates of hospitalization and death. Another study found that losartan, an angiotensin II receptor antagonist, was less effective in lowering blood pressure in blacks than in whites, when taken alone.³⁴

Conversely, the thiazide diuretics appear to be more effective antihypertensives in blacks than in whites. When used alone, hydrochlorothiazide (Esidrix and others) has been found to be more effective in treating hypertension in blacks than in whites, according to the review by Burroughs and colleagues.¹⁰ One

double-blind study of 1292 men with hypertension found that younger black patients were more responsive to hydrochlorothiazide and calcium channel blockers than were white patients.³⁵ And a recent consensus statement from the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks³⁶ acknowledged that both thiazide diuretics and calcium channel blockers are likely to be more effective in treating hypertension in black patients than in white patients.

Studies on the use of β -blockers for the treatment of hypertension have also shown ethnic variation in drug response.^{35,37} The aforementioned consensus statement also cautions that monotherapy with β -blockers is likely to be less effective in treating hypertension in blacks than in whites.³⁶ In a recent literature review, Schaefer and colleagues reported that studies have shown that blacks may need higher doses of β -blockers, including propranolol (Inderal), than those typically prescribed for whites.³⁸ In contrast, studies have shown that Asians usually require lower doses of propranolol than whites do to achieve a therapeutic response.

CULTURAL AND LIFESTYLE FACTORS

Tobacco and alcohol use, both of which may be influenced by cultural and genetic factors, may affect an individual's drug response. Strickland and colleagues noted that the use of tobacco or alcohol may increase or decrease the rate at which a drug is metabolized and cleared.²⁷ A review by Frackiewicz and colleagues stated that smoking has been shown to decrease serum levels of traditional antipsychotics such as chlorpromazine and fluphenazine; this may be caused by the effects of smoking on liver enzymes.²⁴ For example, in one man with schizophrenia the plasma levels of olanzapine dropped and his condition rapidly worsened when his smoking increased from 12 to 80 cigarettes a day.³⁹ The researchers hypothesized that heavy smoking activated the liver enzyme CYP1A2, the main enzyme involved in olanzapine metabolism. And in another study, plasma levels of clozapine in smokers were approximately 80% of the levels in nonsmokers.⁴⁰ A literature search revealed no relevant research on smoking in different populations.

A related concern is adherence to treatment. One large study of people with hypertension found that

Hispanics were less likely than blacks or whites to continue taking medication as prescribed, although the researchers could not account for the difference.⁴¹ Lin and Smith, in discussing how adverse effects often contribute to nonadherence, point out that some drug effects "could be interpreted as either negative or positive" depending on the patient's beliefs and expectations.¹² For example, discussing one research team's study of Chinese patients who were bipolar and receiving lithium, they note the finding that "unlike Western patients, the Chinese rarely complained of 'missing the highs' and regarded polydipsia, polyuria, and weight gain as part of the therapeutic effect." But the Chinese patients also attributed lethargy and poor memory to the drug, although the control group experienced these symptoms at similar rates. If such issues are not taken into account, clinicians might misinterpret a pattern of poor compliance by a particular group as decreased drug efficacy.

Culture-bound syndromes can further complicate evaluation of drug response.²⁸ Culture-bound syndromes are specific clusters of symptoms or patterns of behavior that are considered abnormal within a given ethnic group but are much more common in some groups than others. It's not yet clear whether culture-bound syndromes overlap with established psychiatric diagnoses or are distinct. One example, according to the U.S. Surgeon General, is *ataque de nervios* (literally, attack of nerves), specific to Hispanics; its symptoms may include "screaming uncontrollably, crying, trembling, verbal or physical aggression, dissociative experiences, seizure-like or fainting episodes, and suicidal gestures."⁴² Clinicians' unfamiliarity with a particular culture-bound syndrome may lead to inadvertent misdiagnosis, ineffective treatment, and inappropriate prescribing.

Other factors that may affect drug response and adherence to treatment include language barriers, clinicians' beliefs and preconceptions, and patients' distrust of the health care system. For example, Lin and Smith report that studies have shown that black psychiatric patients have been more likely to be diagnosed with schizophrenia than whites with the same symptoms, and this has been linked to clinician bias.¹² Moreover, according to the U.S. Surgeon General, blacks are more likely than whites are to receive higher dosages of psychotropic drugs, even though research indicates that blacks metabolize such drugs more slowly.⁴³ This can lead to more severe adverse effects and less stringent adherence.

NURSING IMPLICATIONS

Nurses need to be knowledgeable about drugs that may elicit varied responses in patients from different ethnic groups, especially the variations in therapeutic dosages and adverse effects. Some patients will have therapeutic responses at lower doses than those typically recommended; careful monitoring may help prevent unnecessary increases in dosage and adverse effects. For example, among Hispanic patients receiving traditional antipsychotics, symptoms may be managed effectively at lower doses than those typically prescribed.²¹ Black patients on lithium need to be monitored for symptoms of drug toxicity, because serum levels of the drug may be higher than in white patients given the same dosage.³⁰ For the same reason, Japanese and Taiwanese patients may require lower dosages of lithium.⁴⁴ The practice of making therapeutic substitutions with medications in the same drug category to contain costs should be approached with caution. Noting that drugs in the same class may vary in how they are metabolized, the review by Burroughs and colleagues called the practice of therapeutic substitution “clinically risky for patients in different nonwhite racial and ethnic groups.”¹⁰ And of course, no two people are alike. Thus nurses must also be alert to individual variations in drug response and be prepared to initiate discussion with the primary provider and others on the team.

Skill in communicating with patients from various cultures is essential. It's best to ask patients specific questions about possible adverse effects, rather than asking general questions or waiting for the patient to voice concerns. For example, Spector noted that most Asian cultures highly value patience and modesty, adding that “the typical Chinese patient rarely complains.”⁴⁵ Pi and Gray observed that Asians with psychological complaints “are likely to express their problems in behavioral or somatic terms rather than in emotional ones.”⁴⁶ Careful observation and specific questions may be necessary to elicit important information. A nurse interviewing a Chinese American patient receiving haloperidol might ask, “Have you noticed any unusual, involuntary movements?” to determine the presence or absence of extrapyramidal effects.

The importance of considering culture when assessing and teaching patients and families is well recognized. Two useful, basic questions are “What do you think caused your health problem?” and “What treatment do you think will help you?”

Several cultural assessment tools have been developed. Leininger's Sunrise Model focuses on seven major areas: educational; economic; familial and social; political; technologic; religious and philosophic; and cultural values, beliefs, and practices. It also considers how lay and professional beliefs and practices affect the patient's experiences of health and health care. Examples of questions a nurse might ask include⁴⁷:

- In what ways have family members or friends influenced your life, especially regarding your health? How have they cared for you, and how would you like them to care for you now?
- How have your spiritual beliefs helped you to face crises or to heal when you or your loved ones are ill?
- In your daily life, do you use a lot of “high-tech” equipment or appliances? How do you think the equipment used here helps or hinders your care?

Similarly, Giger and Davidhizar's Transcultural Assessment Model considers six areas: communication, space, social organization, time, environmental control, and biologic variations.⁴⁸ It too offers numerous sample questions. For example, an assessment of a patient's communication style includes voice quality, pronunciation and enunciation, use of silence, and use of nonverbal cues; an assessment of the patient's relationship to space includes considering his comfort with proximity to other people and objects and preferred distance during conversation. (For more on cultural assessment, see Resources.)

Determining the patient's language preferences for spoken and written communication is the first step. A language barrier that impedes a nurse's ability to obtain an accurate patient history can contribute to misdiagnosis; one that hampers patient and family teaching can undermine management of the patient's illness. For example, a patient who can't understand the instructions for his drug regimen may not adhere to it; if this isn't recognized, the drug regimen may be needlessly altered. Patients and families also need to know how to identify the major adverse effects of the drugs they're taking and instructions regarding whom to contact if such effects occur.

If an interpreter is needed, one should be provided by the facility. (The Office of Minority Health's National Standards for Culturally and Linguistically Appropriate Services in Health Care [www.omhrc.gov/clas/finalcultural1a.htm] states that using the patient's friends or family members as interpreters is not recommended; one reason is that the

Actions for Nurses

- Learn about drugs that are likely to elicit varied responses in people from different ethnic groups, as well as the potential for adverse effects.
- Conduct a cultural assessment with each patient.
- Ask the patient direct, specific questions to reveal the presence or absence of potential adverse effects of medications.
- Monitor the patient and document findings carefully; it may be possible to maintain therapeutic benefit at a lower dosage of a given drug.
- Keep cultural context in mind when planning education for patients and families.

RESOURCES

Center for Cross-Cultural Research

www.ac.wvu.edu/~culture

The Cross Cultural Health Care Program

www.xculture.org

Diversity Rx

www.diversityrx.org

National Center for Cultural Competence

<http://gucchd.georgetown.edu/nccc>

Transcultural C.A.R.E. Associates

www.transculturalcare.net

Transcultural Nursing Society

www.tcns.org

patient may not be comfortable disclosing certain symptoms or behaviors to them.) In some cases the patient may be fluent in speaking a language but not in reading or writing it. Nurses may also need to become aware of the different terms patients use to describe their illnesses. In our experience, for example, African American patients often refer to hypertension as “high blood” and anemia as “low blood.” A cultural assessment can yield other important information such as dietary preferences, customs related to alcohol and tobacco use, and the use of herbal products. Finally, to become culturally competent, nurses also need to explore their own perspectives, including any assumptions or misconceptions they may have.

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