Genetic Variations in Response to Medications: Looking at the Implications for Minority Elders

by Richard Levy and Jean Polatsek

Genetic, environmental and cultural factors influence variations in drug response among elders from different racial and ethnic backgrounds. The special needs and drug responses of racial and ethnic minority patients have traditionally been undervalued or ignored. These patients may be subject to greater health risks if they are prescribed drugs that are less effective for them. In addition, substantial dosage adjustments may be necessary to avoid overdosing or underdosing.

The factors determining racial and ethnic variations in response to medications are complex and interdependent. Environmental factors such as climate as well as lifestyle choices such as smoking or alcohol consumption may have a profound effect on the way the body handles drugs. Cultural or psychosocial factors may affect a patient’s adherence to a drug regimen, thus influencing the effectiveness of the drug. However, most of the variability in drug effects among different racial and ethnic groups.

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clinical effectiveness and side-effect profiles of many drugs important in treating age-related diseases. Most studies have concentrated on cardiovascular medicines, including beta-blockers, diuretics, calcium channel blockers and ACE inhibitors, and on drugs used to treat mental illness, such as antidepressants and antipsychotics. Painkillers such as acetaminophen and codeine, as well as antihistamines and alcohol, also show varying physiological effects among different racial and ethnic groups.

Due to genetic variations, there can be significant differences in how proteins are encoded—and thus how drugs are metabolized—among racial and ethnic groups. Variations occur in all human genes; some of these variations alter the functioning of proteins. Encoded proteins that may show variation include the enzymes controlling the rate of drug metabolism and the proteins involved in drug response or disease progression.

Genetic variations alter the structure of drug-metabolizing enzymes by making them either less effective or more effective. Thus, people who carry these variations are either slow metabolizers or fast metabolizers of the drugs handled by that enzyme. A drug may become more highly concentrated in the bloodstream of poor metabolizers, which can result in stronger or longer drug action and side effects. Conversely, the drug is less concentrated in the bloodstream of fast metabolizers, resulting in weaker or briefer drug action or side effects.

Tests are now being developed to assess the levels of enzymes in the body that metabolize drugs used for cancer chemotherapy. Individual variations in the levels of these enzymes determine both the efficacy and toxicity of the drugs. Patients who are deficient in these enzymes may suffer severe, potentially fatal toxicity when exposed to standard doses of these medications, whereas chemotherapy may be less effective for patients with an excess of the enzymes. Other genetic tests are being evaluated for applications in treatments for Crohn’s disease, rheumatoid arthritis and kidney transplantation.

Pharmacogenetics research is also targeting a liver enzyme responsible for the metabolism of nearly 25 percent of all drugs, including many cardiovascular agents, antidepressants, antipsychotics and morphine derivatives. By testing for the level of this (continued on back)
enzyme, physicians can determine the correct dosage for their patients. For example, patients with a deficiency in this enzyme metabolize the antidepressant nortriptyline slowly and can tolerate only one-tenth the normal dosage. But patients who have inherited an ultra-rapid metabolism may require as much as five times the normal dose to receive a therapeutic effect.

Variations in the gene controlling this liver enzyme differ in frequency among ethnic and racial groups. Five to 10 percent of African Americans and Caucasians and one to two percent of Asians have inherited the gene deficiency and are poor metabolizers. Interestingly, some African populations are rapid metabolizers.

Researchers hope to use pharmacogenetics testing to predict the effectiveness of nonpharmaceutical interventions as well. For instance, patients with high blood pressure are often advised to follow a low-salt diet, even though this intervention is effective in only a small percentage of patients. A test is now being developed to determine whether a patient carries a variant of a gene that controls salt retention.

Pharmacogenetics could be very beneficial in predicting drug interactions and adverse reactions. This knowledge would be especially useful for treating elders and the chronically ill, who are at particular risk for drug interactions due to interventions involving multiple medications, as well as age-related changes in body functions. Pharmacogenetics testing also will be valuable in assessing those diseases for which treatment response is difficult to evaluate, such as asthma, Alzheimer’s and depression.

Since different medications in the same drug class are often processed by different metabolic pathways, drugs of a given class may differ in their susceptibility to genetic differences in metabolism. In addition, the underlying basis of the disease may differ among racial groups, and some medications will be more effective than others in certain racial groups.

In light of these differences, drug therapy for specific populations and patients should be individualized to achieve the most effective health outcomes. Physicians should resist pressures to apply “cookbook” drug therapy that does not take into account the racial or ethnic origin of their patients. Physicians also should be alert to atypical drug responses or unexpected side effects—especially with cardiovascular or psychiatric drugs. Dosage adjustments may be required.

Healthcare institutions and insurers should limit the practice of therapeutic substitution of alternative medications. Because of genetic variations in drug metabolism, racial and ethnic minority patients are subject to greater risks if they are prescribed an “equivalent” drug. In addition, substantial downward dosage adjustments may be necessary in some cases. Conversely, standard doses of some classes of drugs may be too low in certain racial and ethnic groups, leading to ineffective disease management and more office and hospital visits.

Other cost-management strategies that limit access to pharmaceuticals, such as drug formularies and tiered co-payments, should be broad and flexible enough to enable providers to make the best choices of drugs and dosages for all patients, regardless of race or ethnic origin.

Although belonging to a certain race or ethnicity changes the probability that an individual will respond as expected to a given drug therapy, race is an imprecise indicator for genetic variations. Advances in technology and increased understanding of genetics will eventually enable healthcare providers to move beyond race and tailor drug therapy precisely to each patient. By taking an individual’s “genetic fingerprint,” it is possible to determine the presence of variations in the genes known to be involved in drug response and thus to provide efficient, more effective healthcare.

Although genetic fingerprinting is already possible, knowledge relating specific gene variations to disease progression and response to specific drugs is just beginning to be developed. Information based on correlations between genetic profiles and data on patients’ medical and drug histories will have a profound impact on how new drugs are developed and used.

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