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Medication Metabolism: Sex and Race Variability

by Ann Gerhardt, MD *December 2016*

I last wrote about drug metabolism, the mechanisms and rate by which our bodies degrade and eliminate toxins, medications and naturally occurring or man-made chemical substances in March 2009 (DrG's MediSense Volume 4-1). I discussed inter-individual differences, but didn't mention sexual or racial differences.

The rapidity with which we clear substances out of our system depends on enzymes that do the clearing. Since it takes a gene to make an enzyme, the amount and activity of those enzymes depend on our genetic make-up. Sex and race are major hereditary differences, and it turns out that they are linked to major differences in ability to degrade a whole variety of substances.

With slower clearance, blood levels build up, a substance's effect intensifies and unpleasant effects may appear at lower doses. With rapid clearance, a typical dose often has no effect, good or bad. There are many substance-clearing enzymes, each with a different function. There's no way to predict clearance, since someone who makes a lot of one enzyme, may make little of another.

It turns out that women are much more likely to clear substances more slowly out of their bodies. This is probably why more women than men identify themselves as 'chemically sensitive.' Many women require lower doses of anti-psychotics, opiate pain killers and digoxin. Compared to men, different anti-depressants work better, aspirin protects better against stroke and less well against heart attack and they respond better to beta-blocker blood pressure medicine. Women are 50-75% more likely to report an adverse effect of a medication.

Race is important since genetic mutations that either speed up or slow down clearance get passed down from one generation to the next. We know that African Americans often need higher doses of many medications to be effective, and that the different races respond better to different blood pressure medications, but that's not absolute. We don't yet know how to predict what a particular individual's response will be, since the genetic pattern of each person in a particular racial group is not identical.

Which brings us to the problem of interpreting studies which were used to prove that a new drug provides a benefit that outweighs risk. Until recently most such studies included mostly or all males, who were mostly Caucasian. Pregnant women were always and women of child-bearing age were almost always excluded. Very few African Americans, Hispanics and Asians were included. How is one to know if a given drug even works in women or non-Caucasian races if they weren't studied?

Though Congress passed the 1993 National Institutes of Health (NIH) Revitalization Act that required enrollment of women in phase 3 drug trials, women made up less than one-quarter of all patients enrolled in 46 clinical trials completed in 2004. There are no requirements for racial diversity in clinical trials.

There has been more alarm, leading to more analysis concerning gender than racial disparity in drug studies. A 2006 study published in *Genome Research* reported that the levels of gene expression differed between male and female mice for 72 percent of active genes in the liver, 68 percent of those in fat, 55.4 percent of the ones in muscle, and 13.6 percent of genes in the brain. Women receive the standard influenza vaccine dose, even though they require half as much for the same level of protection. Blood and tissue concentrations of

eleven new medications in women are up to 40 percent off of levels in the average Caucasian male.

Lately the NIH and scientific journals are pushing scientists to analyze results by gender, age and racial subgroups, but often a trial doesn't have enough of each group to lead to meaningful analysis. So doctors blithely prescribe the studied starting dose to everyone and hope that it helps without hurting. Regardless of what starting dose a doctor chooses, patients should speak up and doctors should listen, to gauge how correct that dose was. ⚕