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Does Sex Make a Difference?

By Linda Bren

When it comes to health risks, sex does matter. Women are twice as likely as men to get multiple sclerosis, rheumatoid arthritis, and migraines. They're also more likely to get cataracts, hepatitis, and thyroid disease. Women experience depression about twice as often as men. And irritable bowel syndrome (IBS) is thought to affect twice as many women as men. Although men have more heart attacks than women, more women die within a year after having a heart attack.

"Despite this increased susceptibility to so many diseases, females across the world have a longer lifespan," says Joseph Verbalis, M.D., clinical director of Georgetown University's Center for the Study of Sex Differences, in Washington, D.C. "We don't know why," says Verbalis, "but that's one of the things we're trying to find out."

Researchers are finding that men and women are different in ways that go beyond their reproductive systems, hormones, and bone structure. They get many of the same diseases, but they may have different symptoms, their diseases may progress differently, and they may respond differently to treatment. While researchers are working to discover the underlying causes of these differences, scientists and regulators at the Food and Drug Administration are working to ensure that drugs and medical devices are safe and effective for both men and women.

Just as one size doesn't fit all, one treatment or test doesn't fit all men or all women. It's important to test drugs and devices in both women and men of different races and ethnicities in clinical trials, says Margaret Miller, Ph.D., manager of scientific programs in the FDA's Office of Women's Health (OWH).

The FDA has regulations and guidance in place to ensure that both sexes are represented in clinical trials, that study results are analyzed by gender, and that medical products are labeled to alert physicians and patients to any difference in the way men and women respond to a product. In addition, the agency is supporting research to identify gender differences that may affect the use of FDA-regulated products.

Gender as a Starting Point

Men and women are different in every organ of the body--;even their skin, says Marianne J. Legato, M.D., a cardiologist and founder and director of Columbia University's Partnership for Gender-Specific Medicine. They are different at the cellular level, and these differences may influence the amount and type of medicine they need to treat a disease. "Dosage is not adjustable simply on the basis of body size anymore," says Legato. "I think we have to look at a whole variety of factors in prescribing dosages that are safe on the basis of gender."

"We know that different people, as individuals, respond to drugs differently," says Miller. "People routinely tell me, ‘Oh, that drug doesn't do a thing for me.'" Some researchers place priority on studying differences in genetic makeup

by individual, not gender, says Miller. They want to determine the exact sequence of DNA in a person's body in order to tailor treatments for that individual. "But even if the DNA is the same, men and women will express it differently," says Miller.

Researchers looking at DNA sequence may think that's a shortcut, says Legato, "which it obviously would be if we can take a slice of people's DNA and decide whether or not they would react appropriately to any medication to which they've not been previously exposed. That would be the ultimate, but I fear that that's years away. I think it would be nice to know the difference between men and women as a starting point."

In 2001, the Institute of Medicine (IOM), part of the National Academy of Sciences, published a report that supported studying potential gender differences during drug development. The IOM concluded that "sex matters"; that is, "being male or female is an important basic human variable that should be considered when designing and analyzing studies in all areas and at all levels of ... health-related research." The IOM defined sex-based differences as biologically based differences in men and women, and described gender-based differences as distinctions shaped by the cultural and social environment. Generally, the FDA does not attempt to determine why men are different from women and refers to any identified difference as a "gender difference."

Drugs and Gender Differences

In 1998, the allergy drug Seldane (terfenadine) was removed from the market, when a safer alternative was approved. It had been discovered that Seldane could cause a life-threatening heart rhythm irregularity when used with certain other drugs. More women took Seldane, and more were reported to have had this heart arrhythmia, called torsades de pointes.

Researchers at the Georgetown Center for the Study of Sex Differences believe that the male hormone testosterone may protect the heart from some types of arrhythmia, says Verbalis. In addition, he says, research has shown that women are at greater risk for torsades de pointes because of their QT interval--;the time it takes for the heart to relax after it contracts to pump out blood. Women often have a longer QT interval than men, and taking certain drugs can further lengthen this interval, thereby increasing the risk of the fatal arrhythmia more in women than in men.

Some drugs are approved to treat a disease based, in part, on patients' reporting of the relief of their symptoms. For example, Zelnorm (tegaserod maleate) is approved only for women to relieve the symptoms of IBS. In clinical trials, more women taking Zelnorm reported relief of their symptoms than those taking an inactive pill (placebo).

IBS, which is found more commonly in women, produces a variety of symptoms. "The challenge in the evaluation of a drug for this disease is to determine if there is a gender difference in the patient's perception of symptoms and evaluation of relief of symptoms," says Joyce Korvick, M.D., acting director of the FDA's Division of Gastrointestinal and Coagulation Drug Products. "The perception of ‘relief' of symptoms in men and women may be very different."

Because IBS is found more often in women, more women than men were enrolled in the clinical trials for Zelnorm. But for the nearly 300 men with IBS enrolled in the trials, Zelnorm was not shown to be effective. "More research regarding men and women's perceptions of specific disease symptoms is needed to ensure that differences seen in clinical trials are meaningful to the gender being studied," says Korvick.

Another drug, Zoloft (sertraline hydrochloride), is approved for both men and women to treat several conditions, including post-traumatic stress disorder (PTSD). This approval was based on clinical trials in which Zoloft showed little effect in men with PTSD, while the drug's benefit over a placebo was clear in the women studied.

"True gender differences in responsiveness may have been one explanation," says Thomas Laughren, M.D., team leader for the FDA's psychiatric drug products group. "However, it should also be noted that the types of PTSD differed in the two groups," he says. Many of the men in these trials had a long-lasting and treatment-resistant PTSD, based on military combat experience, compared to many of the women who tended to have a more acute form of PTSD, based on recent physical abuse.

Scientists aren't sure why some drugs work better in one gender than in the other. But they do know that differences may occur in the way men and women absorb certain drugs into the bloodstream, distribute them to the body's tissues, break them down, and rid them from the body. The way the body handles a drug is known as

pharmacokinetics (PK), and was the subject of an FDA study.

FDA researchers examined 300 drug applications submitted to the agency between 1994 and 2000. More than half of these applications contained information on the effect of gender on PK. The PK was the same for 80 percent of the drugs in which PK was studied. But for the other 20 percent of the drugs, the PK was different.

"There must be some reason for this difference," says Miller. "That's where research comes in. We want to understand the biology and the mechanism enough to predict what's going to be in the 80 percent group and the 20 percent group. Then we can predict how a product's safety or effectiveness will be influenced in each gender."

Shiew-Mei Huang, Ph.D., deputy director for science in the FDA's Office of Clinical Pharmacology and Biopharmaceutics, says that drug metabolism plays an important role in the way men and women respond to drugs. An enzyme known as cytochrome CYP3A helps metabolize many drugs, and studies have shown that women have more cytochrome CYP3A in the liver, says Huang. Some drugs or dietary supplements, for example, St. John's wort, increase the activity of this enzyme, which makes the drugs break down faster. This rapid breakdown reduces the amount of the drug in the body, decreasing its effectiveness in women.

The reverse scenario may also occur: A drug could slow down enzyme activity, causing too much of the drug to build up in the body and resulting in more side effects.

But biology can't explain all the differences in the way men and women respond to drugs, cautions Huang. Other factors, such as medication use, must be considered. "A recent survey showed that women, in all age groups, tend to take more medications, including dietary supplements, than men," says Huang. This difference may put women at more risk for certain drug interactions than men.

Medical Devices and Gender Differences

Men and women may also respond differently to certain medical devices and the procedures in which they are used. Several FDA studies have focused on identifying some of these differences.

In 2003 and 2004, FDA researchers studied more than 150,000 people with suspected heart disease and found that women had about twice the risk of men for local complications after cardiac catheterization. In the catheterization procedure, a slender tube is inserted into a large artery in the leg (femoral artery) and is threaded up through the body to the heart to diagnose or treat narrowed heart arteries that block blood flow.

"The study was done to look at risks associated with hemostasis devices," says Dale Tavris, M.D., M.P.H., an FDA epidemiologist specializing in preventive medicine. These devices are used after cardiac catheterization to prevent continued bleeding of the femoral artery where the catheter is inserted.

We don't know why complications, such as hemorrhaging, occurred more in women, says Tavris. "There's speculation that it may be due to blood vessel size or hormonal differences. And the risk applies whether or not the hemostasis devices are used." Further information is needed to understand these occurrences, says Tavris, before we can determine whether any changes to the catheterization procedure or to hemostasis devices or their labeling are appropriate.

An FDA-sponsored study at Boston University involves men and women with diabetes who are using blood glucose monitors at home to test their blood several times a day. Researchers are looking for any differences in testing blood drawn from the fingertip or from another part of the body, since newer glucose monitors use blood samples from alternate body areas. "We found that the fingertip can have a different glucose value from an arm or leg, especially when sugar levels are changing rapidly, for example, after a meal or after exercise," says Jean Cooper, D.V.M., director of the Division of Chemistry and Toxicology in the FDA's Center for Devices and Radiological Health. The study is continuing to determine whether gender might be a factor in this difference in glucose values.

The FDA now requires glucose monitors to carry a warning label cautioning against using alternate sites when glucose levels are changing rapidly. If a manufacturer can show in clinical trials that its device doesn't demonstrate this variance, the warning is not required.

Studies of Both Sexes

In 1977, an FDA guidance said that women able to become pregnant should not participate in the early phases of drug studies, with an exception for studies of potentially life-saving drugs. The exclusion reflected the concern that if a woman became pregnant, the baby might have birth defects.

Over more than two decades, the FDA has worked to ensure that both women and men are represented fairly in clinical trials involving drugs, biologics such as vaccines and blood products, and medical devices.

In 1988, the agency issued guidance to drug makers asking that the safety and effectiveness data in drug applications be analyzed according to gender, age, and race. And, in 1993, the agency issued its Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, known as the gender guideline.

When the gender guideline was published, the FDA also revoked the 1977 restriction on women of childbearing age in early drug studies and reiterated the need to include patients of both sexes in the development of drugs, biologics, and medical devices. The guideline also recommended that drug companies analyze separately men's and women's responses to drugs.

Attention to potential gender differences became part of a larger agency effort to ensure that the safety and effectiveness of drugs are adequately studied in people who represent the full range of patients who could use the drugs when approved. In a 1998 regulation known as the Demographic Rule, the FDA again addressed the importance of collecting data on clinical trial volunteers by gender, race, and age. The regulation required companies to analyze the data to look for possible differences in effectiveness, safety, and dose-response and to submit this information in applications for new drugs. It also required reporting demographic data in annual reports during a drug's investigation phase.

A regulation in 1999 gave the agency the authority to halt studies of new drugs to treat life-threatening diseases if clinical trials excluded women solely because they could become pregnant.

"The Demographic Rule and gender guideline represent our commitment to looking at possible differences in various subgroups' response to drugs, whether men and women, black and white, old and young," says Robert Temple, M.D., director of the FDA's Office of Medical Policy. "The guidance tells drug sponsors what our expectation is and what we're looking for."

So far, a small number of differences have been found in the way men and women respond to drugs, says Temple. An FDA study reviewed gender-related labeling for 171 new drugs that were approved for both males and females from 1995 through 1999. Labeling for two-thirds of the drugs contained some statement about gender, although only 22 percent described actual gender differences and none of these differences were considered significant enough to recommend any change in dosage for one gender.

"But just knowing that is useful information," says Miller. "You know you can take these drugs without a higher risk because of your gender."

The FDA is also working to revise drug labeling so that both consumers and health care providers can better understand important information about a drug. A proposed FDA rule will require prescription drug labels to contain "highlights" in a prominent place. The highlights will discuss the more serious and common side effects and significant gender differences found in clinical trials.

Continuing Efforts

The FDA's Office of Women's Health is funding research within the agency to examine gender differences--;particularly in the areas of heart disease, obesity, and HIV--;that are important for the agency to consider in regulating medical products.

In one project funded by the OWH, scientists within the FDA's Center for Biologics Evaluation and Research are studying the replication of HIV, the virus that causes AIDS, in human blood cells from male and female blood donors.

By infecting the blood cells with HIV in a culture medium and then adding various sex hormones, scientists are learning more about the influence of gender on the concentration of the virus. They are also studying the effect of sex hormones on certain antiviral drugs used to treat HIV.

"Some of the things we're looking at may affect when treatment should be started in men and women," says Andrew Dayton, M.D., Ph.D., an FDA research medical officer. And it may give us preliminary insight into how gender might affect response to HIV treatments, he adds. This information may help in designing clinical trials to test the effectiveness of HIV treatments in men and women.

In another initiative, the OWH is developing an innovative knowledge management approach to make better assessments in groups of people (subpopulations) to protect patient safety. The Demographic Information and Data Repository (DIDR) was mandated by Congress in 2002 to monitor the inclusion of women in clinical trials and to study gender differences and variability in response to medical products.

Katherine Hollinger, D.V.M., M.P.H., a senior health promotions officer in the OWH, says the DIDR will help the agency to look at groups of people--;including groups characterized by gender, race and ethnicity, older people, and children--;in a more informed way. "It will allow us to better look at subpopulation issues and differences in drug response that may affect safety and effectiveness," says Hollinger. "And it will allow us to not only track inclusion of women and other populations in clinical trials, but to monitor the types of trials women, children, or the elderly are participating in and identify patterns that are observed."

Other benefits of the agency-wide DIDR include helping the agency to design better studies for new products, enabling more efficient and informed reviews and approval decisions, and allowing better assessments of product labeling.

Part of the problem in looking at study data to determine subpopulation differences in response to medical products is the lack of standard approaches and terminology used in individual studies. The agency is working with the pharmaceutical industry and standards organizations to establish standardized approaches to labeling, study data, and study protocols that will be used in the DIDR to protect the safety of women, men, children, and older people of every race and ethnicity.

Men, Women, and Disease Risk

Heart attack	Men have more, but women are more likely to die within a year after a heart attack; women tend to get heart disease seven to 10 years later than men
Stroke	Women have fewer strokes, but are more likely to die from them than men; women are generally older than men when they have a stroke
Depression	Twice as common in women
Migraine	Three times more common in women
Hearing loss	More common in men
Nearsightedness (myopia)	More common in women through age 60
Irritable bowel syndrome	More common in women
Cancer	Cancer of the lungs, kidneys, bladder, and pancreas are more common in men; thyroid cancer is more common in women
Osteoporosis	More common in women
Rheumatoid arthritis	Two to three times more common in women
Gout	More common in men

Lupus	Nine times more common in women
Fibromyalgia	Nine times more common in women

National Institutes of Health

Men, Women, and Heart Disease

Heart disease is the leading cause of death in the United States for both men and women, according to the American Heart Association. "But the normal heart is different in men and women," says Marianne J. Legato, M.D., a cardiologist and founder and director of Columbia University's Partnership for Gender-Specific Medicine. "Women's hearts beat faster, even during sleep," she says. And women have different proteins in the heart cells.

"Some data suggest that the whole physiology of the coronary arteries and what keeps them open and what causes them to go into spasm might be significantly different in men and women," says Legato, adding that some women have had heart attacks without any of the fatty buildup of plaque seen in the coronary arteries in most people with heart attacks.

And the symptoms of a heart attack may be different. "Twenty percent of women will not have the 'typical symptoms' of chest pain radiating down the left arm," says Legato, "but will instead describe nausea, profound sweating, and shortness of breath and pain in the upper abdomen."
