

CHAPTER 2

Using Medicine Safely

Most people assume that the effects of prescription drugs are the same for everyone. But an ever-increasing number of studies show that the safety and effectiveness of many widely used drugs vary depending on the sex of the user. In fact, eight of 10 drugs removed from the market by the U.S. Food and Drug Administration (FDA) between 1997 and 2000 posed greater health risks to women than they did to men, according to a report by the General Accountability Office, Congress's nonpartisan audit agency. While sex and medicine issues are still a fairly new concept, it is becoming increasingly clear that physicians and patients should consider a patient's sex when choosing a drug therapy and deciding on dosages.

Safety Differences in Drugs Based on Sex

To take just one example of sex-based differences in drug therapy, common medications, including antibiotics, antihistamines, antidepressants, antipsychotics, and some heart medications, alone or in combination, cause more women than men to develop potentially fatal irregular heart-beat or arrhythmias.

These drugs may act by prolonging the QT interval, the part of the electrocardiogram (EKG) that represents the time it takes for the heart to relax after each beat. Physicians can measure the length of the QT interval in fractions of a second. If it takes longer than normal, it is called a prolonged QT interval. In rare cases, QT prolongation can cause a life-threatening heart rhythm disturbance, called torsade de pointes, and sudden death. In other cases the prolongation does not have serious consequences. The findings suggest that women, doctors, and pharmacists should be alert to cardiovascular side effects brought on by drugs or combinations of drugs.

Pregnancy poses special concerns for women taking medicine. For example, we are learning more about the potential risks of anticonvulsant drugs, which are used by more than a million American women with epilepsy and millions more to treat chronic medical problems affect-

ing the central nervous system, including migraine, severe pain caused by damaged nerves (neuropathic pain), and bipolar and associated mood disorders.

While the majority of women who become pregnant while taking these medications deliver healthy babies, new research shows that some anticonvulsants increase the risk of major malformations (including heart, spinal cord, and cleft lip/cleft palate abnormalities) in fetuses exposed to them during the mother's pregnancy. The Epilepsy Foundation urges women to increase their chances of a successful pregnancy and long-term health by discussing medicine options and possible therapeutic changes with their health care providers before pregnancy. This advice should be followed for women taking other medicines as well.

Other Sex Differences

In addition to potential sex differences in the safety profile of medications, sex differences in the effectiveness of certain drugs have been demonstrated. For example, researchers at the University of California at San Francisco, led by Jon Levine, MD, found that morphine-like painkillers, called kappa opioids, provide more powerful and longer-lasting relief to women than they do to men. In fact, at some doses kappa opioids can actually make the pain worse for men and afford phenomenal pain relief to women.

General anesthesia, drugs that render a person unconscious during surgery, can also behave differently in men and women. At least two studies suggest that women may be less responsive to anesthesia than men. The research shows that women wake up three to four minutes faster than men after taking the same dose of medication per pound of body weight. Women also tend to suffer more side effects, such as headaches, nausea, and vomiting.

Why the Response to Drugs Differs

Exactly why drugs affect men and women differently remains unclear. And, in fact, the answer may turn out to be different for every class of medication. Nonetheless, research points to a number of possible mechanisms for these sex-based differences.

The varying rates at which men and women metabolize drugs may be involved. Studies show that some liver enzymes involved in processing the drugs are more active in women than they are in men, which may affect the levels of drug in the body, drug effectiveness, or the severity of its

side effects. In addition, evidence suggests that a drug's ability to enter some cells in the body may vary between the sexes, which could lead to differences in overall activity of the drug.

Anatomy also affects the way drugs are processed. On average, women have lower body weight, smaller organ size, reduced blood flow, and a higher proportion of fat than men. Overall differences in hormonal activity between the sexes affect the way drugs are processed, absorbed, and cleared by the body as well.

In addition, organs seem to function differently depending on whether they are inside a male or female body. Evidence suggests that "female" kidneys are slower to act than "male" kidneys, a difference that may affect how fast the body gets rid of certain drugs. In addition, liver functioning, which can influence the incidence of adverse events, may vary among men and women. What's more, the rate at which drugs pass through the gastrointestinal system, which affects how much of the drug is absorbed into the bloodstream, seems to differ between the sexes.

Building Awareness

Despite mounting evidence that men and women respond differently to the same drug, most physicians and patients are still not aware that sex matters when medications are prescribed. Why the lack of awareness? One of the reasons is that the FDA and the pharmaceutical industry only recently began to analyze the effects of sex on safety data. In fact, reporting of sex-based data analyses in medical journals, while increasing, is still not routine. This shortcoming of the system keeps sex-specific risks as well as benefits buried beneath heaps of other data.

Women are at higher risk of adverse drug reactions (ADRs) than men, in part because they are more likely to use more than one medication or dietary supplement at any one point in time. A recent review of 48 studies in the United Kingdom revealed that ADRs to newly marketed drugs are 60 percent more common in women than they are in men. This sex difference was observed in all women older than age 19. Other studies have found less pronounced, yet significantly higher risks of ADRs among women.

Women need not look further than their own medicine cabinet for potentially problematic combinations. For instance, oral contraceptives, when taken in combination with the antibiotics rifampin, tetracycline, or penicillin, can fail and result in pregnancy. Considering that women suffer from urinary tract infections (UTIs) more than men do, women should be aware that some antacids can inactivate drugs often prescribed for UTIs, called fluoroquinolones, allowing infections to progress unchecked.

Similarly, because depression affects more women than it does men, there is a greater potential for women to suffer serious consequences when combining selective serotonin reuptake inhibitors (SSRIs) with other types of antidepressants, pain medications, or illegal drugs such as ecstasy and cocaine.

Herbal and Dietary Supplements

Dietary supplements, used more often by women than men, can also interact with other drugs to cause serious problems. And because there are no regulatory requirements for testing most of these compounds in humans, doctors and pharmacists know very little about their risks. Although no FDA-reviewed data exist regarding the risks associated with combining dietary supplements and drugs, numerous reports have indicated that administering some of these compounds together may be harmful. For example, a number of herbs have been shown to interact with heart medications and blood thinners like warfarin. The FDA has specifically warned women who take birth control pills against the concurrent use of Saint John's wort because it decreases the effectiveness of oral contraceptives. Combining Saint John's wort with antidepressants; some cough syrups; a protease inhibitor used to treat HIV/AIDS; the commonly used chemotherapy drug, irinotecan; and the heart medication, digoxin, can also cause serious ADRs.

How to Get Information

Pharmacists can help women avoid undesirable effects of medications by providing them with information about the drugs they are taking. The Public Citizen Health Research Group in Washington, D.C., suggests that women ask their pharmacists for FDA-approved drug information, which contains data on drug interactions. The FDA-approved drug information may supplement the information provided in computer-generated leaflets. All over-the-counter (OTC) medications should also contain an FDA-approved insert. Pharmacists should emphasize to women that, although the FDA-approved inserts provide additional information about the drug, the information is geared to a scientific audience.

The FDA suggests that women also use the following guidelines to help prevent undesirable side effects and interactions:

- ◆ Tell your doctor about everything you take, including prescription and nonprescription drugs and dietary supplements.

- ◆ Stop taking all herbs at least two weeks before surgery, because many interfere with anesthesia and affect blood clotting.
- ◆ Drugs may interact with certain foods and beverages, so ask your doctor or pharmacist if you should make any dietary modifications.
- ◆ Let your doctor know about any side effects you may experience. Keep track of them when you take your medications.

—VIVIANA SIMON, PHD, AND EILEEN RESNICK, PHD