# Sex-Based Differences in Drug Activity

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**Physiologic differences between men and women affect drug activity, including pharmacokinetics and pharmacodynamics. Pharmacokinetics in women is affected by lower body weight, slower gastrointestinal motility, less intestinal enzymatic activity, and slower glomerular filtration rate. Because of delayed gastric emptying, women may need to extend the interval between eating and taking medications that must be absorbed on an empty stomach. Other physiologic differences may affect medication dosages. For example, because renal clearance is slower in women, some renally-excreted medications, such as digoxin, may require a dosage adjustment. Pharmacodynamic differences in women include greater sensitivity to and enhanced effectiveness of beta blockers, opioids, selective serotonin reuptake inhibitors, and typical antipsychotics. Additionally, women are 50 to 75 percent more likely than men to experience an adverse drug reaction. Because women are prone to torsades de pointes, medications known to prolong the QT interval should be used with caution. Women should receive lower dosages of digoxin and have lower serum concentration targets than men because of higher mortality rates. (*Am Fam Physician*. 2009;80(11):1254-1258. Copyright © 2009 American Academy of Family Physicians.)**

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The physiologic differences between men and women play an important role in disease prevalence and outcomes. For example, women are more likely than men to develop cataracts, depression, hepatitis, irritable bowel syndrome, migraines, multiple sclerosis, rheumatoid arthritis, and thyroid dysfunction *(Online Table A)*. Men are more likely to experience myocardial infarction (MI), although women are more likely to die within a year following an MI. Despite the increased susceptibility to many diseases, women consistently live longer than men.[1] Sex-related differences also have important implications for drug activity, including pharmacokinetics and pharmacodynamics.

## Pharmacokinetics

Pharmacokinetics involves the rate and extent of drug movement through the body, including absorption, distribution, metabolism, and excretion. Several physiologic differences between men and women may account for variations in pharmacokinetics, which can affect the dosages of medications with narrow therapeutic indices.[2]

### ABSORPTION

Variations in gastrointestinal motility, gastric pH, and enzymatic activity affect the absorption of oral medications. Women secrete less gastric acid and tend to have slower gastrointestinal transit times than men.[3] Because of this, medications that require an acidic environment for absorption (e.g., ketoconazole antibiotics) may have lower bioavailability in women. This can hinder a medication's effectiveness unless it is administered with an acidic beverage.

A prolonged gastrointestinal transit time can diminish the absorption of medications such as metoprolol, theophylline, and verapamil.[4,5] One study found that the absorption of enteric-coated aspirin was delayed in women following a meal.[6] Therefore, women should wait longer after eating before taking medications that must be administered on an empty stomach. Examples of these medications include ampicillin, captopril (Capoten), cilostazol (Pletal), demeclocycline (Declomycin), felodipine, levothyroxine, loratadine (Claritin), and tetracycline.

The absorption of alcohol also differs between men and women. After consuming the same concentration of ethanol, women will have a higher blood alcohol level than men. This difference in absorption and bioavailability is caused by enhanced activity of the gastrointestinal enzyme alcohol dehydrogenase, which produces faster ethanol degradation in men.[7]

**SORT: KEY RECOMMENDATIONS FOR PRACTICE**

| *Clinical recommendation* | *Evidence rating* | *References* |
|---|---|---|
| For the treatment of depression, men respond better to tricyclic antidepressants and women respond better to selective serotonin reuptake inhibitors. | C | 21-23 |
| Women require lower dosages of antipsychotic medications to control symptoms. | C | 24, 25 |
| Opioids produce a stronger analgesic response in women compared with men. | C | 26, 28 |
| Women have an increased response to beta-blocker therapy. | C | 29 |
| Aspirin therapy has a better protective effect against stroke in women and against myocardial infarction in men. | C | 30 |
| Women with heart failure have an increased risk of mortality when using digoxin therapy. | C | 34, 35 |

*A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.*

### DISTRIBUTION

Drug distribution in the body is influenced by several factors, including body mass index (BMI), body composition, plasma volume, and plasma protein-binding capacity. Men are typically heavier, and have a higher BMI and larger organs than women. These differences should be considered when calculating loading or bolus dosages.[8] Women should receive smaller doses to mitigate unnecessary adverse reactions. Medications that require loading-dosage calculations include class I and III antiarrhythmics, aminoglycosides, chemotherapeutics, digoxin, heparin, lidocaine (Xylocaine), and thrombolytics.[2,8]

Women have larger fat stores than men, which may account for greater volumes of drug distribution, depending on a drug's hydrophilic or hydrophobic properties. Lipophilic medications, such as benzodiazepines[9] and neuromuscular blockers,[10] have a longer duration of action in women because they have larger volumes of adipose tissue than men. Additionally, women are 30 percent more sensitive to neuromuscular blockers and require 22 percent smaller dosages than men.[10] Benzodiazepines also should be initiated at lower dosages in women. Hydrophilic substances, such as alcohol[2,11] and fluoroquinolone antibiotics,[12] distribute into smaller volumes in women, producing higher initial plasma concentrations and greater effects.

### METABOLISM

The initial phase of metabolism oxidizes, reduces, or hydroxylates compounds through the cytochrome P450 system. Although many medications are processed through phase I hepatic metabolism, warfarin (Coumadin) is one of the few to demonstrate a difference in dosage requirement based on sex. Studies indicate that women need between 2.5[13] and 4.5 mg[14] less warfarin per week than men.

Phase II metabolism reactions produce polar conjugates of parent drugs or phase I metabolites for renal excretion through glucuronidation, sulfation, acetylation, or methylation. These metabolic processes are generally accelerated in men, causing some medications to clear faster, including acetaminophen,[15] caffeine,[2,15] digoxin,[16] doxorubicin (Adriamycin),[17] fluorouracil,[2] levodopa,[2] mercaptopurine,[2] and propranolol (Inderal).[2,18]

### EXCRETION

Three aspects of excretion affect renal clearance: glomerular filtration, tubular secretion, and tubular reabsorption. Glomerular filtration rate (GFR) is often estimated using body weight, sex, and serum creatinine. Although some differences between men and women are eliminated by adjusting for weight, GFR remains consistently higher in men.[2] After adjusting for body size, GFRs are 10[19] to 25 percent[8] slower in women.

Medications that are excreted unchanged in the urine are cleared slower in women.[2] For example, digoxin[16,19] and methotrexate[2] are primarily eliminated renally, and have approximately 13 and 17 percent slower clearance in women, respectively. Several other medications have decreased renal clearance in women, including aminoglycosides,[2] cephalosporins,[2,19] fluoroquinolones,[2,19] and vancomycin,[19] as well as the anticonvulsants gabapentin (Neurontin)[20] and pregabalin

(Lyrica).[20] To account for variations in clearance, women should receive lower dosages of these medications based on GFR.

## Pharmacodynamics

Pharmacodynamics is the study of drug mechanism of action, including the physiologic and biochemical effects on the body, and the relationship between drug concentration and the rate and extent of pharmacologic response. Therefore, in any given blood concentration, a drug may invoke variations in response, including differences in effectiveness or safety. Some differences in medication effects between men and women, and subsequent recommendations are listed in *Table 1.*

### ANTIDEPRESSANTS AND ANTIPSYCHOTICS

Men and women respond differently to antidepressant and antipsychotic agents. Although there appears to be no difference in depression symptom severity, women generally respond better to selective serotonin reuptake inhibitor (SSRI) therapy, especially sertraline (Zoloft), compared with tricyclic antidepressants, such as imipramine (Tofranil).[21,22] This may be because women produce more tryptophan and less cortisol when exposed to SSRI therapy.[23] Conversely, men respond better to tricyclic antidepressant medications than SSRIs.[22,23]

Sex can also influence the pharmacodynamics of antipsychotic medications. The onset and severity of symptoms differ between men and women, with men having more severe symptoms, more hospitalizations, and longer hospital admissions.[24] Women exhibit better responses to typical antipsychotic medications, such as haloperidol (formerly Haldol) and perphenazine, whereas men commonly require twice the dosage of women to control symptoms. This is attributed to variations in drug metabolic clearance between sexes.[25]

### OPIOIDS

Estrogen can influence pain pathways, alter pain perception, and affect response to certain drug classes. Because estrogen is present in substantially higher levels in women than in men, women tend to exhibit lower pain thresholds, increased pain ratings to standardized stimuli, and lower tolerance to pain.[26] Women also demonstrate a greater analgesic response to opioids. To achieve equivalent pain relief, men require a 30 to

**Table 1. Differences in Medication Effects Between Women and Men**

| *Drug class* | *Effect* | *Recommendation* |
|---|---|---|
| Aspirin | Poorer platelet inhibition and heart attack protection in women; poorer stroke prevention in men | Consider using higher dosages in women for secondary prevention after a cardiovascular event |
| Beta blockers | Enhanced lowering of blood pressure and heart rate when exercising in women | Monitor blood pressure and heart rate |
| Digoxin | Increased mortality in women | Women require a lower dosage and a lower target serum concentration of 0.8 ng per mL (1.02 nmol per L) |
| Opioids | Greater analgesic response in women | Men require a 30 to 40 percent greater dosage of morphine than women |
| Selective serotonin reuptake inhibitors | Enhanced effect in women | Preferred therapy in women with depressive symptoms |
| Tricyclic antidepressants | Reduced effect in women | Choose alternative with improved effectiveness in women |
| Typical antipsychotics | Enhanced effect in women | Lower dosage in women or increase dosage in men |

40 percent greater dosage of morphine.[27] Sex differences have been attributed to dimorphism in central opioid metabolism or in opioid action at the cellular level.[28] Women also are more likely to experience greater sedative properties and respiratory depression from opioids.

### BETA BLOCKERS AND ASPIRIN

Beta blockers, particularly metoprolol,[29] produce a greater pharmacodynamic response in women. No differences in half-life have been observed between men and women; however, women taking metoprolol demonstrate a greater reduction in systolic blood pressure and heart rate while exercising.[29] These differences are caused by a higher plasma drug concentration in women.[29]

Studies have found differences in the therapeutic profile of aspirin for primary prevention of cardiovascular events. In one analysis, women taking aspirin experienced MI at the same rate as women taking placebo, although there was significant protection against stroke.[30] Conversely, men taking aspirin showed a significant decrease in MI, but no appreciable change in stroke occurrence. Bleeding events were increased in men and women taking aspirin.[30] Another study found that aspirin use in women was associated with a lower rate of complete platelet inhibition when taken as secondary prevention after a cardiovascular event.[31] These results may be attributed to effects from testosterone in men and the use of hormone therapy in women.[31]

### ADVERSE DRUG REACTIONS

Women are 50 to 75 percent more likely than men to experience an adverse drug reaction.[32] These differences may be caused by increased polypharmacy, increased drug bioavailability, and greater sensitivity to medication.[33] Torsade de pointes is a serious adverse drug reaction that is more common in women than in men. Women naturally have a longer QT interval than men and are predisposed to torsade de pointes.[33] Medications known to prolong the QT interval and potentially induce torsade de pointes include antiarrhythmics (e.g., amiodarone [Cordarone], disopyramide [Norpace]), antibiotics (e.g., erythromycin, moxifloxacin [Avelox]), antidepressants (e.g., imipramine, amitriptyline), and antipsychotics (e.g., chlorpromazine).[32,33]

After the release of the 1997 Digitalis Investigation Group study,[34] digoxin use increased in selected patients with heart failure. Later, a post hoc subanalysis found that women taking digoxin had a significantly higher mortality risk compared with women taking placebo.[35] This outcome was not observed in men. When treated with digoxin, women experienced a higher rate of mortality from any cause compared with men treated with digoxin (5.8 percent absolute rate) and compared with women taking placebo.[35] Although explanations for this increased rate of mortality among women are unknown, lower serum concentrations of less than 0.8 ng per mL (1.02 nmol per L) are recommended.[36]

Women also demonstrate a six- to eightfold increase in drug-induced rash from human immunodeficiency virus medications nevirapine (Viramune) and efavirenz (Sustiva), and experience higher rates of drug-induced liver disease from antiepileptic drugs.[20] One reason for these differences could be that women generally have stronger immune systems and produce more immunologic products, such as antibodies.[20]

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