

# Sex and Gender Differences

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## Learning Objectives

1. Distinguish between the terms sex and gender to foster their correct usage.
2. Describe sex/gender differences in disease presentation, morbidity, and mortality.
3. Analyze the differences in disease epidemiology and presentation in women for common conditions.
4. Apply the changes in drug pharmacokinetics and pharmacodynamics across a woman's lifespan to individualize medication therapy.
5. Evaluate the potential reasons for the differences in adverse drug effects between women and men.

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To achieve optimal pharmacotherapy in women, healthcare providers must understand the effect of **sex** and **gender** on diseases and medications. Presently, the scientific evidence has documented many sex/gender differences that are clinically important to healthcare providers. This chapter is an overview of sex/gender differences with an emphasis on pharmacokinetics and pharmacodynamics. Some of the more important differences in biology that are due to sex will be highlighted, as well as some differences in epidemiology of common diseases in women vs. men. Within the other clinical chapters, further exploration and details are provided for sex/gender differences. Recommendations for individualizing pharmacotherapy to account for sex/gender differences are also provided in those chapters.

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## Terminology

The sex and gender of a person, whether woman or man, profoundly affects her/his biology, behavior, perceptions (e.g., self, life), and health. *Sex* is a biologic classification determined by reproductive organs and is usually the result of having two X chromosomes for women, or one X and one Y chromosome for men. Sexual differences between women and men manifest not only at a reproductive level in the person, but are also expressed at basic cellular and molecular levels. *Gender*, on the other hand, is a person's outward expression (i.e., clothing, behavior, etc.) of being a woman or man and is influenced by society, the environment, and personal cultural beliefs and experiences.<sup>1</sup> Confusion about the correct use of these terms—sex vs. gender—occurs in both the scientific and lay press. When the two terms are used interchangeably or incorrectly, barriers are created as a result of misunderstandings that require clarification and result in slowed progress for research in this area.

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## The Institute of Medicine Report on Sex as a Contributor to Human Health

In 2001, the Institute of Medicine released a publication that explored the sexual differences in many diseases from genetic, physiologic, and environmental perspectives.<sup>1</sup> Many examples were reviewed that show how sex affects the physiology and epidemiology of diseases and how sex influences the drugs used to treat diseases in women and men. Three consistent topics were woven throughout this publication, including the importance of sex as a biologic characteristic, the improvement in research knowledge on the biology of sex differences, and an acknowledgment of barriers that exist for those who conduct research in this area.<sup>1</sup>

## CASE PRESENTATION

### Patient Case: Part 1

M.A. is a pleasant, sleepy, 87-year-old Lebanese woman who lives at home with her daughter, son-in-law, and two grandchildren. M.A. has been a U.S. citizen for the last 30 years and fully understands the English language. She presents for follow-up care at your geriatric care clinic with no specific symptoms. The daughter accompanies M.A. to the appointment and reports that her mother is less steady on her feet and seems more confused in the morning. The daughter further describes that her mother is often groggy and asks the clinic pharmacist to evaluate her medication regimen. Three months ago, M.A. was started on ziprasidone for afternoon and evening agitation that was believed to be due to her Alzheimer's disease.

**HPI:** M.A. has a history of multiple medical conditions that include diabetes mellitus type 2, osteoarthritis of knees and left hip, hypertension, atrial fibrillation, and probable Alzheimer's disease.

**PMH:** M.A. has a pacemaker for a history of a cardiac arrhythmia.

**Family and social history:** M.A. was married at 21 years of age and remained married until her husband's death 3 years ago. M.A. became confused and disoriented after the death of her husband and subsequently moved to her daughter's house, where she presently resides.

**Medications:** Aspirin 81 mg daily, Coumadin 4 mg daily, calcium with vitamin D supplements 2 times daily with food, glyburide 5 mg daily, lisinopril 5 mg daily, acetaminophen 1,000 mg 3 times daily, donepezil 10 mg at bedtime, ziprasidone 40 mg at bedtime, and docusate 200 mg at bedtime.

**Allergies:** No known drug allergies.

**Vital signs:** Blood pressure 128/74 mm Hg (without postural changes), heart rate 76 beats/minute, afebrile, and respirations 16/minute. M.A. weighs 48 kg and is 5 feet tall.

**Physical exam:** M.A.'s physical exam is unchanged from her last visit 3 months ago. Her cardiac, pulmonary, and gastrointestinal exams are normal. M.A. continues to have a small amount of swelling and hypertrophy of both knees with good strength in all extremities. M.A. is not able to cooperate with the Mini Mental State Exam (MMSE) because of sedation. Her MMSE from 3 months ago was 25/30.

All labs are normal with the following significant findings: sodium 139 mEq/L, potassium 4.3 mEq/L, blood urea nitrogen 28 mg/dL, creatinine 1.2 mg/dL, glucose 102 mg/dL, A1C 5.4%, and the international normalized ratio (INR) 2.7.

At a cellular level, differences in basic biochemical processes exist that are the result of X or Y chromosome characteristics, which might be independent of hormonal differences between women and men. For instance, testosterone is presumed to be the reason men have a larger skeletal and muscle mass than women even though the effect of testosterone on genes has not been determined.<sup>2</sup> Recently, gene expression in human skeletal muscle was explored by examining common skeletal and muscle genes in healthy women and men.<sup>2</sup> The women and men in this study were from two age groups: a younger group between 20 and 29 years and an older group between 65 and 75 years of age. Both the younger and older women had a twofold higher expression of two important genes than men: one that encodes growth factor proteins and another that regulates myostatin activity. The growth factor receptor bound 10 gene (GRB10) inhibits insulin-like growth factor signals, whereas the activin A receptor IIB gene (ACVR2B) increases the effect of myostatin, which significantly influences muscle size.<sup>2</sup> Even though the women were from both pre- and postmenopausal age groups, their high expression of GRB10 and ACVR2B was consistent. This research is generating hypotheses that can be tested to further understand the sexual differences in the biology of women and men. In addition, research at the molecular and cellular level helps us to understand one of the premises of the Institute of Medicine report: that "every cell has a sex."<sup>1</sup> This is an important fact to both understand and control for in all aspects of research that will be applied to healthcare in people.

Language may serve as an example of a sex difference that extends from cellular biology and human function through recovery from disease. Women are believed to use both cerebral hemispheres for language, whereas men have a localized organization in the left hemisphere.<sup>3</sup> Echoplanar functional magnetic resonance imaging was used to study the language differences between 19 healthy women and 19 men.<sup>3</sup> Tests

of **orthographic**, **phonologic**, and **semantic language** skills were done equally well between the women and men. The women used both the right and left inferior frontal gyrus to complete these tasks, whereas the imaging scans showed that the men had markedly localized activity in the left inferior frontal gyrus.<sup>3</sup> This difference in language organization in the brain may explain why women are more likely to recover speech than men after a left-sided stroke.<sup>1</sup> However, even though there may be evidence for improved speech recovery in one specific type of stroke, overall, women have poorer recovery from stroke than men. For instance, in a prospective cohort of 373 patients with stroke in Michigan, at 3 months after hospital discharge, women were less likely to achieve independence in activities of daily living, to improve stroke quality of life measures, and to improve scores of thinking, language, and energy.<sup>4</sup> To provide better healthcare for women and men, healthcare providers need to understand the sex differences in biology and disease epidemiology, as well as the social factors that influence the spectrum of illness and recovery. Although sex might explain most of these differences, gender is also important when weighing the role of social influences on disease presentation, treatment, and recovery.

## Sex/Gender Differences in Mortality

Men have higher age-adjusted death rates for all causes combined, as well as for almost every specific cause, than women.<sup>5</sup> Cardiac disease has been the number-one cause of death for both women and men since the 1950s (Table 7-1).<sup>5-7</sup> However, for both women and men, the death rate for cardiac disease has declined 64% from 1950.<sup>5</sup> Men continue to have significantly higher death rates for cardiac disease than women (260.9 vs. 172.3 per 100,000 people, respectively in 2005).<sup>5</sup>

Both women and men have sex-specific cancers as the leading cancer diagnosis; however, both sexes are more likely to die as a result of lung cancer (Table 7-1). The overall age-adjusted death rate for cancer declined by 15% for both women and men from 1990 to 2005.<sup>5</sup> This improvement is predominately due to gains in successful treatment of cancer in younger women and men.

In the U.S., disparities in mortality statistics exist by race and sex (Figure 7-1 and Figure 7-2).<sup>5</sup> For men, the disparities in mortality values by race are mainly due to injuries and violence.



### Therapeutic Challenge:

Many women are more fearful of dying from breast cancer than cardiovascular disease. Why is this? How can women be educated and motivated to follow heart-healthy lifestyles to prevent cardiovascular disease and death?

## Sex/Gender Differences in Disease Morbidity

Although many similarities are found with causes of death, many diseases affect women and men differently. The incidence of cardiovascular disease is similar between women and men, but women with cardiovascular disease tend to be 10–15 years older than men upon diagnosis and are more likely to die from myocardial infarctions (see Chapter 30: Cardiovascular Disease).<sup>6,7</sup> Women also present with different symptoms of angina. Instead of having the classic angina symptoms of left-sided chest pain or pressure, women more commonly report nausea, indigestion, chest discomfort, upper back and jaw pain, and profound exhaustion. Because of these differences in presentation, standard treatments for acute myocardial infarctions like aspirin, beta-blockers, thrombolytics, and percutaneous transluminal coronary angioplasty are not provided as often to women. More recently, differences in standard treatments between women and men with cardiovascular disease have diminished significantly.<sup>6,7</sup> Women also have a higher mortality rate with coronary artery bypass grafts, higher bleeding rates with thrombolytic therapy, and lower success rates with initial angiography.<sup>7</sup>

The rate of cigarette smoking has declined in men but increased in women even though evidence suggests that women may be more susceptible to lung damage from cigarette smoking. Women who smoke have a significantly higher diagnosis rate for lung cancer despite differences in smoking history and body size (see Chapter 36: Substance-Use Disorders).<sup>1,6,8,9</sup> Another disease strongly linked to cigarette smoking, chronic obstructive lung disease, is the leading cause of death worldwide, and the actual number of deaths in women are greater than in men.<sup>10</sup> The rate of cigarette smoking by women in developing countries continues to rise. Women are

**Table 7-1. Differences in Leading Causes of Death, Cancer Diagnosis, and Cancer Death in the U.S. Between Women And Men<sup>a,5-7</sup>**

Women		Men	
Leading Causes of Death	Deaths (per/100,000 U.S. Residents)	Leading Causes of Death	Deaths (per/100,000 U.S. Residents)
1. Heart disease	172.3	1. Heart disease	260.9
2. Cancer	155.6	2. Cancer	225.1
3. Stroke	45.6	3. Unintentional injuries	54.2
4. Chronic lower respiratory diseases	38.1	4. Stroke	46.9
5. Alzheimer’s disease	36.1	5. Chronic lower respiratory diseases	51.2
6. Unintentional injuries	25.0	6. Diabetes	28.4
7. Diabetes	21.6	7. Influenza and pneumonia	23.9
8. Influenza and pneumonia	17.9	8. Suicide	18.0
9. Kidney disease	14.6	9. Kidney disease	13.8
10. Septicemia	12.3	10. Alzheimer’s disease	13.1
Leading Cancer Diagnosis	New Cases (per/100,000 U.S. Residents)	Leading Cancer Diagnosis	New Cases (per/100,000 U.S. Residents)
1. Breast	121.0	1. Prostate	159.3
2. Lung	47.2	2. Lung	69.3
3. Colorectal	40.7	3. Colorectal	54.8
Leading Causes of Cancer Death	Cancer Deaths (per/100,000 U.S. Residents)	Leading Causes of Cancer Death	Cancer Deaths (per/100,000 U.S. Residents)
1. Lung	40.5	1. Lung	69.0
2. Breast	24.1	2. Prostate	24.5
3. Colorectal	14.8	3. Colorectal	20.9

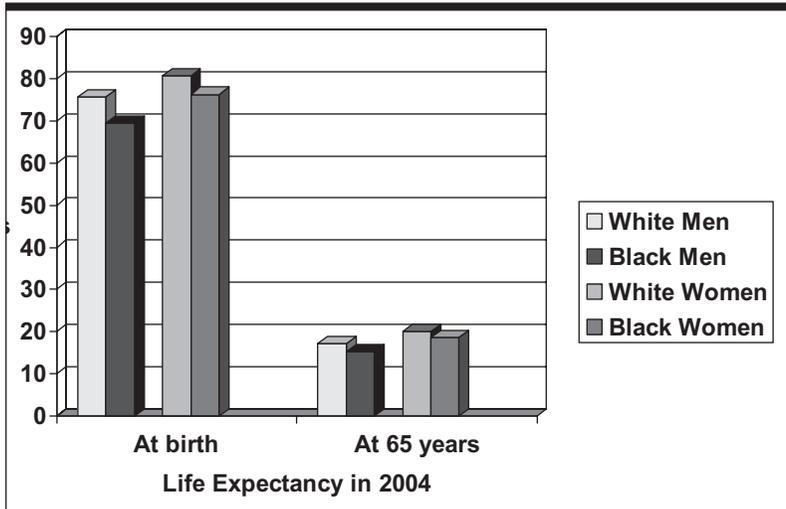
<sup>a</sup>Age-adjusted death and incidence rates per 100,000 U.S. resident population in 2005.

more susceptible to lung damage from some of the other causes for chronic obstructive lung disease, such as pollution and occupational exposure.<sup>11</sup> Women are not diagnosed as early with chronic obstructive lung disease, nor do they receive treatment that successfully controls their pulmonary symptoms as often as men.<sup>11</sup>

Common bone and joint diseases, such as osteoporosis and osteoarthritis, primarily affect women (see Chapter 40: Bone and Joint Disorders). Of the 10 million patients diagnosed with osteoporosis, 80% are women.<sup>12</sup> Osteoporosis also has appreciable

morbidity differences between the sexes. In patients older than 50 years, 50% of women will suffer an osteoporosis-related fracture as compared with 25% of men. These fractures tend to be devastating, because 20% of patients with a hip fracture die within 1 year.<sup>12</sup> Osteoarthritis affects more than 16 million people in the U.S. and is the leading cause of disability in older women.<sup>13</sup> Some evidence suggests that women do not receive surgical joint replacement as often as men, even though women have greater disease severity. In a population-based study in Canada, 48,218 residents with hip or knee pain were

Figure 7-1. Life expectancy by sex and race.<sup>5</sup>

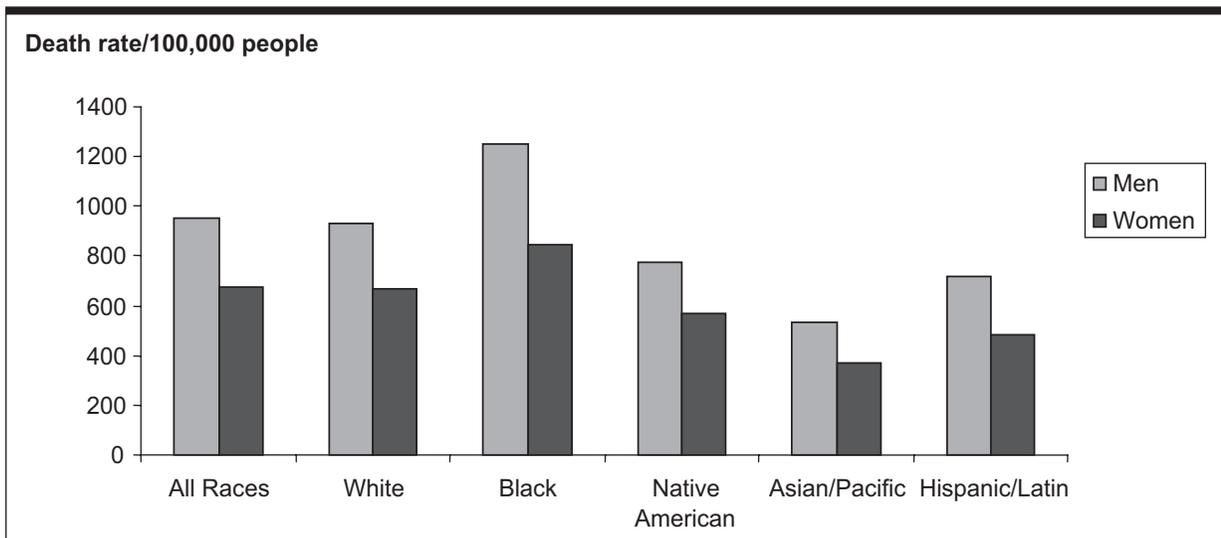


evaluated for the use of total joint arthroplasty.<sup>14</sup> After adjustments for disease prevalence and willingness to undergo surgery, women were 3 times more likely as men to have a medical need for surgery but were less likely to talk with their physicians about surgery (adjusted odds ratio 0.63;  $p < 0.01$ ) or to undergo arthroplasty (adjusted odds ratio 0.78;  $p < 0.001$ ).<sup>14</sup> In Canada, where access to healthcare is more equal than in the U.S., it is hard to explain the large disparity in arthroplasty rates for women with osteoarthritis. Some gender-based reasons could exist, such as a fear in women to experience any amount of disability

from surgery, given that they tend to either live alone or to be caretakers of family. Women and men might perceive surgical risk and pain differently. The results could also suggest a possibility of unconscious selection bias by the healthcare providers.<sup>14</sup> Education directed at all individuals about osteoarthritis and osteoporosis and their treatments is needed to ensure optimal patient outcomes.

Many immunological diseases occur more often in women than men (see Chapter 37: Immunity and Autoimmune Diseases and Chapter 41: Neurological Disorders). Women are afflicted with rheumatoid

Figure 7-2. Age-adjusted death rates by sex and race in 2005.<sup>5</sup>



arthritis, scleroderma, myasthenia gravis, and multiple sclerosis at a rate that is 2–3 times greater than that for men.<sup>1</sup> There are even larger differences in the rates of occurrence for systemic lupus erythematosus, Hashimoto thyroiditis, Graves' disease, autoimmune hepatitis, and primary biliary cirrhosis, with women experiencing these diseases up to 10 times more often than men.<sup>1,15</sup> The reason for the marked differences in occurrence in autoimmune diseases between women and men is controversial and confounded by sex, biology, and rate of exposure of agents in the environment that might induce disease. Because women and men have a similar immune response after immunization and to treatment of infection, sex-based causes are under investigation.<sup>15</sup>

Some immune-based diseases fluctuate in severity during times of hormonal change in women, leading to theories that circulating estrogen plays a role in the severity of disease. Case reports support the notion that during states of hormone castration or supplementation, disease remission or exacerbation may occur. For instance, patients with rheumatoid arthritis and multiple sclerosis may enter disease remission during pregnancy.<sup>16</sup> One theory to explain the hormonal effect suggests that estrogen is permissive to growth of autoimmune clones of cells, placing girls and women at risk during a time of environmental exposure.<sup>17</sup> The X chromosome in women might also be a possible reason for the differences in disease by inactivation, modulation, or imprinting of genetic information. Lupus remains an active model of research to explain sex differences because of the marked male-to-female ratio of disease occurrence, long latency period for disease expression, and genetic risk factors. One proposed theory suggests three sequential steps that begin at conception and culminate during menarche. First, a girl may be at risk because of genetics or through in utero factors, and she is subsequently exposed to an etiologic agent, such as a virus, during childhood. The final step would occur during puberty, when estrogen may permit autoimmunity (or a lack of testosterone to restrain autoimmunity), leading to the development of clinical symptoms of lupus in young women.<sup>18</sup>

Even though investigating the effect of sex in health-related research is a recent phenomena, there are presently many known differences in disease incidence, presentation, diagnosis, and treatment outcome between women and men. Consideration of the influence of this powerful biologic variable is needed for the optimal healthcare for women.



### **Therapeutic Challenge:**

**When evaluating a study about sex (biological) differences, what confounders need to be controlled to eliminate gender (social) differences?**

## **Pharmacokinetic Changes over a Women's Lifespan**

Pharmacokinetic parameters vary for many reasons related to age and maturity of the person, sex, and genetic background (Table 7-2).<sup>1,19-54</sup> Sex-related differences in pharmacokinetics will include both chromosomal and hormonal differences. The following section will summarize pharmacokinetics in infants, girls, menstruating women, pregnancy and childbirth, and elderly women. Oftentimes, sex-related effects on pharmacokinetics are not well investigated, requiring the healthcare provider to make dosing decisions based on data published exclusively in men or data that are combined for both women and men.

### **INFANTS AND CHILDREN COMPARED WITH ADULTS**

The basic pharmacokinetic properties of absorption, distribution, metabolism, and elimination are strongly influenced by pediatric growth and development, which affects medication dosing for girls. There are no known sex differences in pharmacokinetics at this age. At birth, the pH of the stomach is neutral; however, acid production begins within minutes of delivery in full-term infants. By 48 hours following birth, the gastric pH decreases to 3. Then, over the next 24 hours, the pH returns to neutral and remains neutral for the following 10 days.<sup>19</sup> Thereafter, gastric pH steadily decreases through the first 2 years of life until it reaches adult values. Preterm infants' initial



### **Therapeutic Challenge:**

**What type of research, data collection, and analyses are required by the Food and Drug Administration related to age and sex for new drug approvals?**

**Table 7-2. Pharmacokinetic and Physiologic Changes Associated with Age, Menstrual Cycle, Pregnancy, and Sex Differences**

	Changes in Pediatrics	Changes During Menstrual Cycle	Changes During Pregnancy	Changes in Elderly Women	Changes Due to Sex <sup>a</sup>
Absorption	<p>↓ Gastric pH<sup>19</sup></p> <p>Gastric emptying time reaches adult times by 6–8 mo<sup>20,21</sup></p> <p>↑ Skin absorption in infants<sup>19,21,22</sup></p> <p>↑ Rectal pH<sup>23</sup></p>	No change <sup>23,26,27</sup>	<p>↓ Motility and intestinal blood flow<sup>31</sup></p> <p>↑ Gastric pH<sup>31</sup></p>	<p>↑ Gastric pH</p> <p>↓ Gastric emptying time</p> <p>↓ Gastrointestinal blood flow</p> <p>↓ or unknown percutaneous absorption<sup>36,37</sup></p>	↓ Gastric emptying time <sup>38-40</sup>
Distribution	<p>↑ Volume of distribution for hydrophilic medications<sup>20</sup></p> <p>↓ Protein binding<sup>21</sup></p>	No change <sup>28-30</sup>	<p>↑ Blood volume</p> <p>↓ Serum albumin levels</p> <p>Thinning of fetal-maternal barrier<sup>32,33</sup></p>	<p>↓ Volume of distribution for hydrophilic medications</p> <p>↑ Volume distribution for lipophilic medications</p> <p>↓ Protein binding<sup>36,37</sup></p>	<p>↑ Volume of distribution for lipophilic medications<sup>1,41</sup></p> <p>↓ Volume of distribution for hydrophilic medications<sup>1,41</sup></p>
Metabolism	Phase I <sup>b</sup> and II <sup>c</sup> metabolism immature until 1 year of age <sup>24</sup>	Variable effects <sup>30</sup>	<p>Phase I</p> <p>↑ Hydrolysis (phenytoin)</p> <p>↓ Oxidation (theophylline)</p> <p>↓ CYP1A2</p> <p>↑ CYP2A6</p> <p>↑ CYP2C9</p> <p>↓ CYP2C19</p> <p>↑ CYP2D6 (third trimester)</p> <p>↑ CYP3A4<sup>34</sup></p> <p>Phase II No change</p>	<p>Phase I Variable influence on CYP activity<sup>36,37</sup></p> <p>Phase II No change</p>	<p>Phase I</p> <p>↑ Oxidation (benzodiazepines)<sup>41-48</sup></p> <p>No change oxidation<sup>41-48</sup></p> <p>No difference CYP3A4 isoenzyme<sup>43,44,49,50</sup></p> <p>↑ CYP1A2<sup>44,50</sup></p> <p>↑ CYP2D6<sup>44,50-52</sup></p> <p>No change in other CYP isoenzymes<sup>53</sup></p> <p>Phase II</p> <p>↓ Conjugation (benzodiazepines)<sup>41-53</sup></p>
Renal Elimination	GFR matures by 2 years of age <sup>22,25</sup>	<p>↓ GFR in early follicular phase</p> <p>↑ GFR in luteal phase<sup>23,26,27</sup></p>	↑ Renal blood flow and GFR <sup>31-35</sup>	↓ Creatinine clearance <sup>36</sup>	↓ Creatinine clearance <sup>54</sup>

GFR = glomerular filtration rate; CYP = liver isoenzymes.

<sup>a</sup>Women compared with men.

<sup>b</sup>Phase I metabolism includes oxidation, hydrolysis, and reduction.

<sup>c</sup>Phase II metabolism includes conjugation, glucuronidation, sulfation, and acetylation.

acid production and following changes are delayed up to 2 weeks. Gastric emptying is delayed for the first few days after birth in all newborns because of a lack of peristalsis and reduced gastric motility.<sup>20,21</sup> However, in infants 6–8 months of age, gastric motility has reached adult values.<sup>21</sup> Other factors to consider in intestinal drug absorption are immaturity

of gut mucosa leading to increased permeability, immature biliary function, reduced first-pass metabolism, and variable microbial colonization.<sup>22</sup> Intramuscular administration is unreliable in neonates because of decreased peripheral perfusion and muscular contraction.<sup>21</sup> Additionally, neonates have less muscle mass, which is associated with severe pain

at the injection site. Absorption through the skin in neonates, especially premature infants, is faster and higher because of an undeveloped epidermal barrier, increased skin hydration, and increased surface area relative to weight.<sup>19,21,22</sup>

Rectal absorption has limited changes that are due to maturation. Rectal pH in children is alkaline but is close to neutral in adults.<sup>21</sup> However, bioavailability may be affected by the first-pass effect. The degree of first-pass metabolism of a rectal-administered drug is determined by local venous drainage and the site of drug delivery. Drugs administered high in the rectum are directly metabolized by the liver, whereas administration in the lower rectum results in local absorption of the drug, which is then delivered systemically before passing through the liver.<sup>25</sup>

In comparison with children and adults, total body water in infants is high (80% to 90% of body weight), whereas adipose content is low (10% to 15% of body weight). The amount of total body water decreases to 55% to 60% by adulthood.<sup>20</sup> Extracellular water content is also different; 45% of body weight in neonates is extracellular compared with 20% in adults, which correlates with larger volume of distribution for hydrophilic drugs. Age-related distribution changes are also observed in protein binding, which is reduced in neonates and infants. Binding proteins in this population are low in concentration and have a lower capacity to bind.<sup>21</sup>

Birth results in dramatic changes in the hepatic circulation and oxygen tension, which may affect hepatic function within the neonatal period.<sup>24</sup> Biliary excretion and hepatocellular uptake are inefficient, and phase I (oxidation) and phase II (conjugation) metabolic enzymes are immature.<sup>24</sup> However, *in vitro* data showed that by 2 months of age, significant amounts and activity of metabolic enzymes were present, and by 1 year of life, they were fully matured.<sup>21,22,24</sup>

Unlike metabolism, maturation of renal function begins during fetal development. Nephrogenesis begins at 9 weeks of gestation, is completed by 34 weeks of gestation, and is followed by postnatal renal blood flow changes. As renal blood flow increases, glomerular filtration rate (GFR) increases during the first few weeks of life from 2–4 mL/min/1.73 m<sup>2</sup> at birth to 70 mL/min/1.73 m<sup>2</sup> in full-term infants and only 20 mL/min/1.73 m<sup>2</sup> in pre-term infants.<sup>22</sup> Premature infants have reduced renal function at birth, and nephrogenesis will continue after delivery. Glomerular filtration rate may exceed

adult values on a kilogram basis around 3 months of age, and it has been shown that glomerular filtration takes approximately 2 years to mature. After 2 years, GFR capacity is similar in children and adults.<sup>25</sup> Tubular secretion is decreased at birth but reaches adult values in about 1 year.

### MENSTRUAL CYCLE-RELATED CHANGES

Limited information has been published in the literature to document the effects of a woman's menstrual cycle on drug pharmacokinetics. Some of these changes are summarized in Table 7-2 and also discussed in Chapter 10: Menstrual Cycle. During menstruation, varying effects on gastric emptying time have been reported, but these changes do not appear to significantly affect drug absorption.<sup>23,26</sup> Protein binding or volume of distribution changes during the menstrual cycle do not affect drug concentrations for ranitidine, theophylline, phenytoin, or nitrazepam.<sup>27–29</sup> With respect to metabolism, several small studies demonstrated that fluctuating hormone concentration during the menstrual cycle produced variable effects on cytochrome P450 enzyme metabolism.<sup>27</sup> Creatinine clearance decreased by 4% to 20% during the first week of the menstrual cycle compared with the luteal phase, although no clinically significant changes occurred for amikacin, theophylline, or tobramycin concentrations.<sup>28–30,32,33</sup> Despite these potential pharmacokinetic changes, none have resulted in any clinically significant effects on medications (i.e., no dosage adjustments).<sup>27</sup>

### PREGNANCY-RELATED CHANGES

Several changes occur during pregnancy that affect pharmacokinetics (see Chapter 23: Drug Principles in Pregnancy and Lactation) that may result in increased or decreased drug concentrations (Table 7-2). Elevated serum estrogen concentrations decrease gastrointestinal motility and increase intestinal blood flow, which increases drug absorption. Drug distribution may increase during pregnancy because of a 40% to 50% increase in blood volume and increased distribution to the fetal circulation from thinning of the placental barrier. Hepatic metabolism can increase and decrease during pregnancy. Progesterone elevations can stimulate increased metabolism of drugs such as phenytoin, resulting in lower concentrations. On the other hand, medications like theophylline can compete with high estrogen and progesterone concentrations for metabolism, resulting in higher drug concentrations. Renal function increases by 25% to 50% during pregnancy from increased cardiac

output, which results in an elevated creatinine clearance.<sup>31-35</sup> These changes can affect drug concentrations of renally eliminated medications, with dosage adjustments required as function continues to change throughout the pregnancy. Many medications, particularly drugs with a narrow therapeutic index, require more frequent monitoring during pregnancy.

### ELDERLY WOMEN

Aging produces significant changes in drug pharmacokinetics that are correlated to changes in physiology. Pharmacokinetic changes that may be related to sex can not usually be separated from pharmacokinetic changes that are due to age, even though the sex differences persist as women get older.

Older people have an increase in gastric pH, a delay in gastric emptying time, and reduced gastrointestinal blood flow.<sup>37</sup> However, because most drugs are absorbed through passive diffusion, these age-related physiologic changes in the gastrointestinal track do not lead to significant changes in the bioavailability of most drugs. Older women continue to have a higher bioavailability for drugs that undergo CYP3A4 metabolism and p-glycoprotein transport, such as midazolam and verapamil.<sup>36</sup> Percutaneous absorption may be less in older people using transdermal drug delivery systems because of atrophy of the epidermis, thinning of the dermis, and a decrease in skin lipid content. Sex-related differences in percutaneous absorption have not been investigated between older women and men, but caution should be exercised for older women who lack a sufficient fat layer (because of physical size or weight) to appropriately absorb medications from transdermal drug-delivery systems.

Drug distribution can be altered in seniors because of changes in body composition that include a decrease in body water content, an increase in body fat, and a decrease in serum albumin. These age-related changes occur in both women and men.<sup>36,37</sup> In addition, older women and men weigh less than younger adults, and white and Asian elderly women tend to weigh the least in comparison with other groups. This has an impact on initial loading doses for older women who are physically small and who are receiving drugs with a narrow therapeutic window like digoxin, antiarrhythmics, and certain antibiotics. Because of a smaller volume of distribution, loading doses in older women should be individualized based on weight. For drugs that are particularly

fat soluble, such as the benzodiazepines, the increase in total body fat leads to a larger volume of distribution and longer elimination half-life. Drug distribution may also be altered because of changes in serum albumin and  $\alpha_1$ -acid glycoprotein concentrations leading to a higher proportion of the free fraction of bound drugs.<sup>37</sup> These changes do not generally affect maintenance dosing of the high-protein-bound and low-extraction-ratio drug phenytoin, but they do create a need to interpret the serum concentrations differently.<sup>36</sup>

Elimination of drugs is less in older people, as well as being generally lower in women. A reduction in liver blood flow will lead to a decrease in metabolism for drugs that are dependent on hepatic blood flow, such as morphine, propranolol, and some hydroxymethylglutaryl coenzyme A reductase inhibitors (e.g., simvastatin).<sup>37</sup> Changes related to aging and sex in metabolism through phase I cytochrome P450 pathways are more complex and are not well studied in older women.<sup>36</sup> Drug elimination by phase II pathways is probably not significantly different between older vs. younger people or by sex. Recent work suggests that reductions in metabolism of drugs through CYP450 enzymes is more related to alcohol intake, smoking cigarettes, genetic differences, and underlying liver disease than to age or sex.

Renal function does decline progressively with age and continues to be further decreased in elderly women vs. elderly men, resulting in the need to lower dosages of renally eliminated drugs. Renal function should be estimated with an acceptable equation—such as the Cockcroft-Gault formula, which adjusts for renal function changes related to both age and sex—to determine the extent of dosing adjustment needed. An ideal formula is not available to estimate creatinine clearance, particularly in older women who may be physically small or have a low serum creatinine. Adjustment of the Cockcroft-Gault formula for body surface area can minimize some of the estimation error.<sup>36</sup> Generally, the formulas are used to estimate renal function to place an older woman into mild, moderate, or severe categories so that proper dosing of medications can occur.

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## Pharmacokinetic Differences That Are Due to Sex

Several differences exist between women and men in pharmacokinetic properties (Table 7-2). Differences in bioavailability, distribution, metabolism, and renal elimination related to sex differences are often



### Therapeutic Challenge:

What impact do the age-related changes have on dosing, efficacy, and safety of opioids in seniors, especially agents such as propoxyphene and meperidine? How do age-related pharmacokinetic changes influence medications placed on the Beer's list of inappropriate medications that should not be used in seniors?<sup>55</sup>

ascribed to variation in body weight, plasma volume, plasma protein levels, cytochrome P450 activity,  $\alpha_1$ -acid glycoprotein activity, and renal clearance.

Drug absorption factors, such as gastric emptying, transporters, and enzymes, have both similarities and differences between the sexes; however, clinical significance of this data has not been determined. To begin, gastric emptying time of both liquids and solids is slower in women, but no difference exists in small intestine emptying time; however, the clinical significance for medications absorbed in the stomach is unknown.<sup>36,38-40</sup> Absorption for most medications is not significantly changed, because most drug absorption occurs in the small intestine.<sup>1,38</sup> Changes in gastric enzymes responsible for drug metabolism are best demonstrated in women, in whom alcohol dehydrogenase activity is lower, leading to higher concentrations of serum alcohol compared with men even after controlling for differences in body size.<sup>56,57</sup>

Differences between women and men in the expression of transporter proteins that influence drug absorption are conflicting. Early literature had disagreement with respect to P-glycoprotein concentration expression between women and men; however, recent work failed to find sex differences when using fexofenadine as a probe for P-glycoprotein.<sup>56</sup> Another recent study analyzing overall sex differences using Western blot technology confirmed that no difference exists between the sexes with P-glycoprotein expression.<sup>43</sup>

The volume of distribution of medications can vary depending on the lipid solubility of the drug and its protein-binding characteristics. Women have a higher percentage of body fat and, as a result, lipophilic medications have a larger volume of distribution.<sup>1,41</sup> Some drugs that are more water soluble, like levofloxacin, fleroxacin, ofloxacin, and fluconazole, have been noted to have higher serum

concentrations, even with adjustments for body mass. This difference may account for an increased incidence of adverse effects of fluoroquinolones in women.<sup>44-47</sup> Serum albumin does not seem to vary by sex; however,  $\alpha_1$ -acid glycoprotein may change in relation to estrogen. Examples of how this may affect drug dosing are not clear.

Several differences exist between the sexes with respect to drug metabolism. Women tend to oxidize faster and conjugate slower but reduce similarly; however, nonbenzodiazepine medications metabolized via oxidation did not demonstrate a difference between women and men.<sup>41,42,48</sup> With cytochrome P450 enzyme metabolism, no overall difference exists between the sexes for activity for the enzyme family 3A.<sup>43,44,49,50</sup> However, when additional medications are administered that can induce CYP3A activity, women may have greater induction of intestinal activity than men, but the clinical significance of this is unknown.<sup>49</sup> Additionally, St. John's wort seems to induce CYP3A4 in women by about 90% vs. 50% in men.<sup>53</sup> Less information is available about the cytochrome P450 isoenzyme 1A2, but clearance might be higher in men than women with respect to clozapine and caffeine.<sup>45,50</sup> Sex differences do not appear in the 2C9 family of enzymes.<sup>44,45-51</sup> Women tended to have higher activity for 2D6 when the probe drug metoprolol was used. Similarly, in patients with high expression for 2D6, women have higher activity, but the clinical significance of these findings is unknown.<sup>44,50-52</sup>

Finally, variations with renal drug excretion have been noted between women and men, which may result in clinically significant differences and risks for adverse events. Women have lower serum creatinine concentrations and creatinine clearance compared with men.<sup>54</sup> Although some equations for calculating creatinine clearance, like the Cockcroft-Gault, adjust for differences in women, many medications do not have separate dosing recommendations for the sexes. The differences in renal function are clinically important because they may increase the risk of adverse events, as with bleeding risk from glycoprotein IIb/IIIa inhibitors in women.<sup>58</sup>

## Pharmacodynamics Differences That Are Due to Sex

Sex-related differences in pharmacodynamics are less documented than sex-induced changes in pharmacokinetics. Often, pharmacodynamic differences are

considered only when a higher rate of adverse drug reactions in women is noticed. Even when a pharmacodynamic difference in women may be a likely cause for a different pharmacologic response, the pharmacokinetic and pharmacogenetic influences are difficult to separate from the pharmacodynamic. Overall differences in the use of a medication between women and men add further bias and confusion when interpreting adverse drug reaction data. The U.S. General Accounting Office published a report on drugs withdrawn from the market for safety reasons from 1997 to 2001. Of the 10 withdrawn medications, eight had higher reported adverse reactions in women than men, and of those eight drugs, four medications likely had a pharmacologic reason for the difference in adverse event (terfenadine, astemizole, mibefradil, and cisapride).<sup>59</sup> QTc-prolongation and torsades de pointes are frequently reported adverse drug reactions for a number of drugs that may not share any chemical similarity. Women have a baseline-corrected QT interval (QTc) that is longer than men, which may add an additional risk factor.<sup>60,61</sup> There are drugs known to have significant differences in adverse reaction profiles between women and men (see Web Resources).<sup>58,61-70</sup>



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Some data suggest that women suffer a higher rate of death when treated with digoxin for chronic heart failure.<sup>71</sup> In a post hoc analysis of the Digitalis Investigation Group Trial, women who were treated with digoxin suffered a rate of death that was higher than men; an adjusted odds ratio of 1.23 (95% confidence interval 1.02–1.47). Men received an average digoxin dose of 0.25 mg and women received 0.22 mg. After adjustment for body mass index, the dose of digoxin was slightly higher for the men than women (0.0093 vs. 0.0084 mg per unit of body mass index, respectively), but digoxin serum concentrations were slightly higher for women than men at 1 month (0.9 ng/mL vs. 0.8 ng/mL, respectively).<sup>71</sup> The serum concentrations of digoxin were the same in women and men at 1 year (0.6 ng/mL), and there were no differences in digoxin toxicity between women and men. The increase in death in women treated with digoxin could be related to pharmacokinetics, pharmacodynamics, or a combination of the two.

Women may respond differently than men when aspirin is used for primary prevention of heart disease

and stroke. In a large primary prevention trial, 100 mg of aspirin every other day for 10 years reduced the risk of stroke but not the risk for myocardial infarction or death from cardiovascular disease.<sup>72</sup> Aspirin used in a similar fashion in men is effective in reducing the risk for myocardial infarction and death from cardiovascular disease but not stroke.<sup>73</sup> This opposite finding for women vs. men may be due to sex-based pharmacodynamics. Aspirin reduces platelet aggregation more in men than women in *in vitro* studies.<sup>74</sup> This effect may be related to the presence of testosterone.

Finally, particular caution must be employed when using drug treatments that place older women at risk for bleeding. Older women who need anticoagulation with warfarin have a higher rate of hemorrhage, even after adjustment for INR, which is likely due to age, genetics, and sex-related changes in pharmacokinetics, pharmacodynamics, and pharmacogenetics.<sup>63</sup> These differences are adjusted in present algorithms that individualize warfarin dosing by reducing the warfarin dosage for all three of these variables. Older women have also experienced higher rates of hemorrhage from thrombolytics, low-molecular-weight heparin, and glycoprotein IIb/IIIa inhibitors.<sup>58,75</sup> The precise cause of the high rate of drug-induced bleeding in older women is not known, but for glycoprotein IIb/IIIa inhibitors, it is likely due to a failure to appropriately adjust the drug dosage based on renal function.<sup>58</sup>

## Summary

Many differences exist between disease incidence, presentation, diagnosis, and outcome to treatment between women and men. Many of these differences are due to the biological consequences of sex, although gender can contribute to and influence diagnosis and treatment differences. Women also have differences in drug pharmacokinetics that occur as they mature and enter adolescence, and that continue



**Therapeutic Challenge:**  
What other medications have pharmacodynamic differences between the sexes?

## Patient Case: Part 2

### Diabetes

**Assessment:** Presently, M.A.'s diabetes is under control; she has a normal blood sugar and meets treatment guidelines for an A1C <7%. Her creatinine clearance is estimated to be 25 mL/min with the Cockcroft-Gault equation.

**Recommendation:** Decrease the dosage of glyburide to 2.5 mg daily.

**Rationale:** Glyburide is metabolized to a renally excreted active metabolite. It is not known if M.A. has impairment in liver function related to sex or age. Although creatinine clearances are not precise in seniors, because of the estimated value, her age, and small size, she most likely has compromised renal function. Hypoglycemia related to accumulated concentrations of glyburide could contribute to this patient's symptoms of unsteadiness and confusion.

**Monitoring:** Home blood glucose checked and recorded daily at varying times and A1C. Review patient's home glucose values and an A1C in 3 months.

**Patient education:** Both patient and family need to be able to recognize and respond to low blood-glucose concentrations.

### Cardiovascular Diseases

**Assessment:** M.A.'s blood pressure is at goal values of <130/80 mm Hg, and she does not experience postural effects upon standing. M.A.'s heart rate is controlled. Her INR is within normal range, but she is receiving duplicative anticoagulation therapy.

**Recommendation:** Continue treatment of her hypertension with lisinopril. Refer her to a cardiologist for discontinuation of Coumadin or aspirin.

**Rationale:** The use of both aspirin and Coumadin is not recommended because the combination in an older woman will increase the likelihood of bleeding.

**Monitoring:** Blood pressure and bleeding. Because M.A.'s blood pressure is controlled, every 6–12-month checks should be adequate. The patient should check for signs of bleeding on a daily basis.

**Patient education:** Both patient and family need to be able to recognize and respond to signs of minor and major bleeding.

### Osteoarthritis and Osteoporosis

**Assessment:** M.A. is receiving a total daily dosage of 3 g of acetaminophen for osteoarthritis management and calcium with vitamin D supplements for

osteoporosis prevention. M.A. does not report pain, although her mobility is reported to be limited.

**Recommendation:** Refer M.A. to a physical therapist for assessment and possible implementation of a therapeutic walking regimen. In this older woman, a trial of a lower dosage of acetaminophen (650 mg 3 times daily) is recommended. Continue the calcium with vitamin D supplementation. Ask family if they would like to have a DXA (dual energy absorptiometry) test done to assess her bone mineral density and need for additional medication.

**Rationale:** It is not known if either age- or sex-related changes in metabolism affect the use of acetaminophen in this case; some limited evidence suggests that acetaminophen is metabolized less in older individuals and less in women than men. M.A. has normal liver function tests.

**Monitoring:** Pain and mobility limitations; liver function tests. Follow-up at routine scheduled clinic visits for osteoarthritis pain assessment and liver function tests as needed while she receives acetaminophen on a regular basis.

**Patient education:** Advise the patient and family to avoid taking more than 3 g of acetaminophen from all sources daily; encourage walking to maintain mobility.

### Alzheimer's Disease

**Assessment:** M.A. has increased confusion, which could be related to disease, medications, and or environment.

**Recommendation:** No change in Alzheimer's medication. Decrease the dosage of ziprasidone, using a tapering process until the drug can be discontinued.

**Rationale:** M.A.'s MMSE score was within normal limits 3 months ago. Alzheimer's disease is a slowly progressing disease; the confusion is most likely not related to disease deterioration and does not warrant additional Alzheimer's medications at this time. The use of atypical antipsychotics for agitation in a patient with dementia is controversial and may lead to an increase in mortality. Ziprasidone is also metabolized by the cytochrome P450 2D6 family of isoenzymes. There are no reports of decreased metabolism of ziprasidone related to age or sex, although this drug has QT prolongation as a side effect. In addition, ziprasidone is a likely cause of increased sedation and confusion in this setting. Nonpharmacologic therapies, such as creating a serene environment and using a consistent daily structure, should be tried first for behavior management, which were not done in this case (beyond scope of this chapter).

**Monitoring:** Night-time agitation, daytime sedation and confusion. Weekly contact with the family to assess for changes in mental state and mood.

**Patient education:** Affirm with the family that Alzheimer's disease is a slowly progressive condition and that any abrupt changes in M.A.'s status should be reported to their healthcare provider.

through their older years, from both sex, hormonal, and maturation influences. Some pharmacokinetic differences are significant and place women at an

increased risk for adverse drug reactions. Pharmacodynamic changes are also important, although less well studied, and explain some of the differences in treatment outcome and adverse effects seen in women. Healthcare providers must carefully weigh the influence of sex on drug and disease parameters to create optimal pharmacotherapy regimens in women.

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## References



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