Pharmacy Tech Topics™

VOLUME 22 NO. 1 | JANUARY 2017

Medication Safety in the Older Adult

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Pharmacy Tech Topics™ (USPS No. 014-766) is published quarterly for $50 per year by the Illinois Council of Health-System Pharmacists, 4055 N. Perryville Road, Loves Park, IL 61111-8653. Phone 815-227-9292. Periodicals Postage Paid at Rockford, IL and additional mailing offices.

POSTMASTER: Send address changes to:
Pharmacy Tech Topics™, c/o ICHP, 4055 N. Perryville Road, Loves Park, IL 61111-8653

LEARNING OBJECTIVES

Upon completion of this module, the subscriber will be able to:

1. Describe the importance of medication safety in a growing population of older adults.
2. Explain age-related changes in drug processing and sensitivity to medication therapy.
3. Recognize medications that should be avoided in older adults.
4. Discuss strategies for improving medication safety in older adults.
5. Identify medication safety concerns in cases that illustrate inappropriate medication use in the older adult.

ACCREDITATION

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This module will provide 2.5 contact hours of patient safety continuing pharmacy education credit for pharmacy technicians.
ACPE Universal Activity Number: 0121-0000-17-001-H05-T | Type of Activity: Knowledge-based
Release Date: 01/01/17 | Expiration Date: 01/01/20 (at 12:00AM CT)

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Medication Safety in the Older Adult

**For definitions of bolded terms, refer to the glossary in Appendix A (page 26-27).*

Introduction: An Aging Nation

According to the United States Census Bureau, the United States (US) population is expected to increase from 319 million in 2014 to 417 million by 2060 with nearly one in five Americans at least 65 years of age by 2030.[1] In fact, the 65 years of age and older population is the fastest growing age group in the US. By 2060, it will reach 98 million people—more than double its size in 2014.[1] With the first of the baby boomers celebrating their 65th birthday in 2011, the biggest surge in the senior citizen population in the US is projected to occur between 2020 and 2030. As this timeframe is quickly approaching, healthcare workers, including pharmacy technicians, will need to be prepared to meet the specialized needs of an aging population.

Older Adults: A Vulnerable Population

With advances in medical and surgical care, Americans are indeed living longer. However, older adults—people 65 years of age and older—are also living with multiple chronic diseases, including heart disease, diabetes, lung disease, dementia, arthritis, and cancer.[2] In order to manage these numerous health conditions, older adults are often subjected to **polypharmacy**, which refers to the use of multiple medications including complex medication regimens and potentially unnecessary medications.[3] One-third of adults over the age of 65 years reportedly take at least five medications, and the highest number of medications are taken by those over the age of 75 years. Nearly half of community-dwelling older adults also use at least one over-the-counter medication or dietary supplement.[4] The number of medications administered in hospitals and nursing homes may be even higher, with two-thirds of older nursing home residents receiving nine or more medications according to data from the Centers for Medicare and Medicaid Services (CMS).[3] The use of numerous medications in any patient, regardless of age, increases the risk for medication errors, drug interactions, and the potential for harm or injury to the patient. If injury results from drug therapy, this is called an **adverse drug event**.[5] In addition to concerns over polypharmacy, the older adult may also have several chronic conditions, see many different physicians and healthcare providers, and use more than one pharmacy.[6,7,8] These and other factors increase the older adult's risk for adverse drug events. Refer to **Table 1** for common risk factors associated with adverse drug events in older adults.

Older adults are more vulnerable to medication-related injury for other key reasons, including age-related changes in the way their bodies process medications—known as **pharmacokinetic** changes—as well as an increased sensitivity and response to certain medications—known as **pharmacodynamic** changes. Impairments in memory, sight, and hearing may also increase the risk of medication mistakes among older adults such as skipping doses or taking medications incorrectly. Emergency room visits and hospital stays due to adverse drug events are also more likely in older adults due to the factors discussed above. Compared to younger adults, older adults are almost seven times more likely to experience a drug-related injury that requires hospitalization.[9] An estimated 99,628 emergency hospitalizations for adverse drug events oc-

Table 1. Risk Factors for Adverse Drug Events in the Older Adult Population[6,7,8]

Age ≥ 85 years old
≥ 5 medications or ≥ 12 doses of medication per day
Multiple chronic conditions
Multiple pharmacies
Multiple prescribers
Dementia
Depression
Recent hospital visit
Routine alcohol use
Low body weight
Poor kidney function
History of adverse drug event
≥ = greater than or equal to

cur each year in the US, and nearly half of these hospitalizations occur in the "oldest old" or those over 80 years of age.[9] Medications that are frequently associated with hospital visits for older adults include drugs that increase risk of bleeding (such as warfarin [Coumadin]—and aspirin), lower blood sugar (such as insulin and oral diabetes medications), lower blood pressure (such as beta-blockers and diuretics), and cause sedation or drowsiness (such as anxiety medications or sleep aids).[9]

Falls are also a common cause of hospitalization, injury, and even death among older adults. Each year in the US, one in three older adults over the age of 65 years falls, and 9,000 of these adults will die annually from fall-related complications.[10] The number of medications as well as specific classes of medications have been associated with falls in older adults. Published literature has suggested that using four or more medications may increase the risk of falls in adults over the age of 65 years living in the community.[11,12,13] Polypharmacy is also associated with falls in hospitalized older adults, and using several medications has been found to increase the risk of hip fracture among nursing home patients who have a history of falling.[11,14] Several different types of medications are also associated with falls in the older adult as seen in **Table 2.** However, the two broadest categories of drugs that are implicated in falls include **psychotropic** medications that cause sedation and affect balance by acting on the **central nervous system**, which houses the brain and spinal cord, or medications that lower blood pressure by acting on the heart and blood vessels, which make up the **cardiovascular system.**[10,11,12,13,14,15] Specific medications affecting these two body systems will be discussed in later sections.

Frail older adults, in particular, are at significant risk for **falls**, hospitalization, and medication adverse effects. **Frailty**, which often occurs with advanced age, is characterized by weight loss, loss of strength and balance, fatigue, impaired memory and function, and dependence on others for care.[16,17] Due to a diminished physiological reserve, frail older adults are less capable of withstanding stress, and therefore, are more vulnerable to adverse drug related effects.[17,18] The frailest older adults often receive the greatest number of medications (recall that nursing home residents tend to have longer medication lists than their healthier, community-dwelling counterparts). With greater prescribing, the potential for inappropriate medication choices—such as psychotropic medications in a patient with a history of falls—also exists. Potentially inappropriate medication prescribing has been reported in up to 20% of community-dwelling older adults, 30% of hospitalized older adults, and as many as half of older adults living in nursing homes.[18] Among these institutionalized elderly, adverse drug events continue to be high and frequently include drug-related falls and confusion. The frequency of adverse drug events in nursing homes likely reflects both prescribing patterns and the frail disposition of the older adults living in these settings.[18]

Contributing significantly to this problem is the exclusion of older adults, particularly frail individuals, from clinical drug trials. However, prescribing decisions for both young and old patients are often based on these clinical trials. When trials are conducted on younger, healthier populations, anticipated drug adverse effects and risks in real life populations of older adults may be severely underestimated.[18] Therefore, medications tested exclusively in younger adults should be used with caution or not at all in older patients. To increase physician awareness about potentially unsafe or inappropriate medications in older adults, expert consensus panels have formulated lists of medications to avoid or use cautiously in the older adult, such as the Beers criteria, which will be discussed in a later section.[19,20,21]

Despite the existence of such useful lists and criteria, one of the most important interventions to minimize risk of adverse drug events is a reduction in the overall number of medications prescribed to older adults.[18] Careful review of the older adult's complete medication list is an important practice to identify potentially inappropriate medications and to reduce polypharmacy. In the hospital, community, or nursing home setting, pharmacists frequently perform medication review, which is a systematic process for evaluating each medication for its potential benefits and harms to the patient, and providing a recommendation for therapy change in light of the patient's conditions, preferences, and social or economic situation.[22] Pharmacy technicians can play a valuable role in helping the pharmacist identify a precise and complete patient medication list, especially in the older adult population due to the sheer complexity and number of medications. Transitions between care settings can also be particularly challenging and represent an important area for proper medication review. Transitions from the hospital to the nursing home and vice versa are subject to medication discrepancies, errors, and adverse medication events.[23]

Table 2. Medications Associated with Falls in Older Adults[10,11,12,13,14,15,19,20,21]	
Medications Acting on the Central Nervous System	*Antidepressants (Tricyclic)*
Benzodiazepines	Amitriptyline (Elavil)
Alprazolam (Xanax)	Desipramine (Norpramin)
Chlordiazepoxide (Librium)	Doxepin (Silenor)
Clonazepam (Klonopin)	Imipramine (Tofranil)
Diazepam (Valium)	Nortriptyline (Pamelor)
Flurazepam (Dalmane)	*Antidepressants (Selective Serotonin Reuptake Inhibitors)*
Lorazepam (Ativan)	Citalopram (Celexa)
Oxazepam (Serax)	Escitalopram (Lexapro)
Sleep Aids	Fluoxetine (Prozac)
Diphenhydramine (Benadryl)	Paroxetine (Paxil)
Eszopiclone (Lunesta)	Sertraline (Zoloft)
Zaleplon (Sonata)	**Medications Acting on the Cardiovascular System**
Zolpidem (Ambien)	*Blood Pressure Medications*
Anti-Psychotic Medications	Amlodipine (Norvasc)
Haloperidol (Haldol)	Clonidine (Catapres, Kapvay)
Olanzapine (Zyprexa)	Doxazosin (Cardura)
Quetiapine (Seroquel)	Hydralazine (generic only)
Risperidone (Risperdal)	Lisinopril (Prinvil, Zestril)
Anti-Seizure Medications	Losartan (Cozaar)
Gabapentin (Neurontin)	Metoprolol (Lopressor, Toprol XL)
Pregabalin (Lyrica)	Minoxidil (Loniten)
Valproate (Depacon, Depakene, Depakote)	Prazosin (Minipress)
Opioids	Terazosin (Hytrin)
Hydrocodone (Norco, Vicodin, Lortab, Lorcet, Hyslingla ER, Zohydro ER)	*Diuretics*
Hydromorphone (Dilaudid, Exalgo)	Bumetanide (Bumex)
Morphine (MS Contin, Avinza, Kadian)	Furosemide (Lasix)
Oxycodone (OxyContin, Roxicodone)	Hydrochlorothiazide (Microzide)
Anti-Parkinsons or Restless Legs Medications	Metolazone (Zaroxolyn)
Carbidopa/Levodopa (Sinemet)	Torsemide (Demadex)
Pramipexole (Mirapex)	*Nitrates*
Ropinirole (Requip)	Isosorbide Dinitrate (Isordil, IsoDitrate, Dilatrate)
*Anticholinergic Medications (See **Figure 2**)**	Isosorbide Mononitrate (Imdur, Monoket)
Oxybutynin (Ditropan, Oxytrol)	Nitroglycerin (Nitrostat, Nitro-Dur, Minitran)
Tolterodine (Detrol)	*Miscellaneous*
Benztropine (Cogentin)	Digoxin (Lanoxin, Digitek, Digox)
This list is not all inclusive but rather provides a sample of medications in each class of medications.	
*Although the association with anticholinergic medications and falls is not clear, these medications have been found to affect gait (walking) speed. This may lead to falls and problems with balance.	

In order to successfully perform medication review or reconciliation in the older adult population, pharmacists and other healthcare providers must have an increased awareness of potentially harmful medications, doses, or combination of medications. Understanding and appreciating specific age-related changes in drug processing and drug response is the first step to recognizing unsafe medications in the older adult population. Therefore, an overview of such changes in drug processing will be provided in the first portion of this module to set the stage for a later discussion of high risk medication classes as well as strategies for improving medication safety in the older adult.

Case 1

Mrs. Smith is an 86-year-old woman brought to Dr. Potter's office by her daughter, Sarah. Sarah lives with her mother and has become very concerned about her mother's deteriorating health. In the last two months, Mrs. Smith has fallen three times. The last fall, two weeks ago, resulted in a trip to the hospital as Mrs. Smith fell on the driveway and sustained several lacerations. Mrs. Smith has multiple chronic conditions including high blood pressure, high cholesterol, heart disease, kidney disease, depression, insomnia, and urinary incontinence (difficulty holding her bladder). In addition to Dr. Potter, Mrs. Smith also sees a heart specialist after her heart attack last year. Sarah helps her mother with her numerous medications, which include:

Aspirin 81 mg by mouth daily for heart disease

Pravastatin (Pravachol) 40 mg by mouth nightly for high cholesterol

Lorazepam (Ativan) 1 mg by mouth at bedtime for insomnia

Amitriptyline (Elavil) 25 mg by mouth daily for depression

Amlodipine (Norvasc) 10 mg by mouth daily for high blood pressure

Metoprolol (Lopressor) 12.5 mg by mouth twice daily for high blood pressure

Oxybutynin (Ditropan) 5 mg three times daily for urinary incontinence

Test Your Knowledge #1

Review Case 1 at left. List Mrs. Smith's risk factors for an adverse drug event. (Refer to Table 1 for a complete list of possible risk factors).

1._____ 5. _____
2. _____ 6._____
3. _____ 7._____
4. _____ 8._____

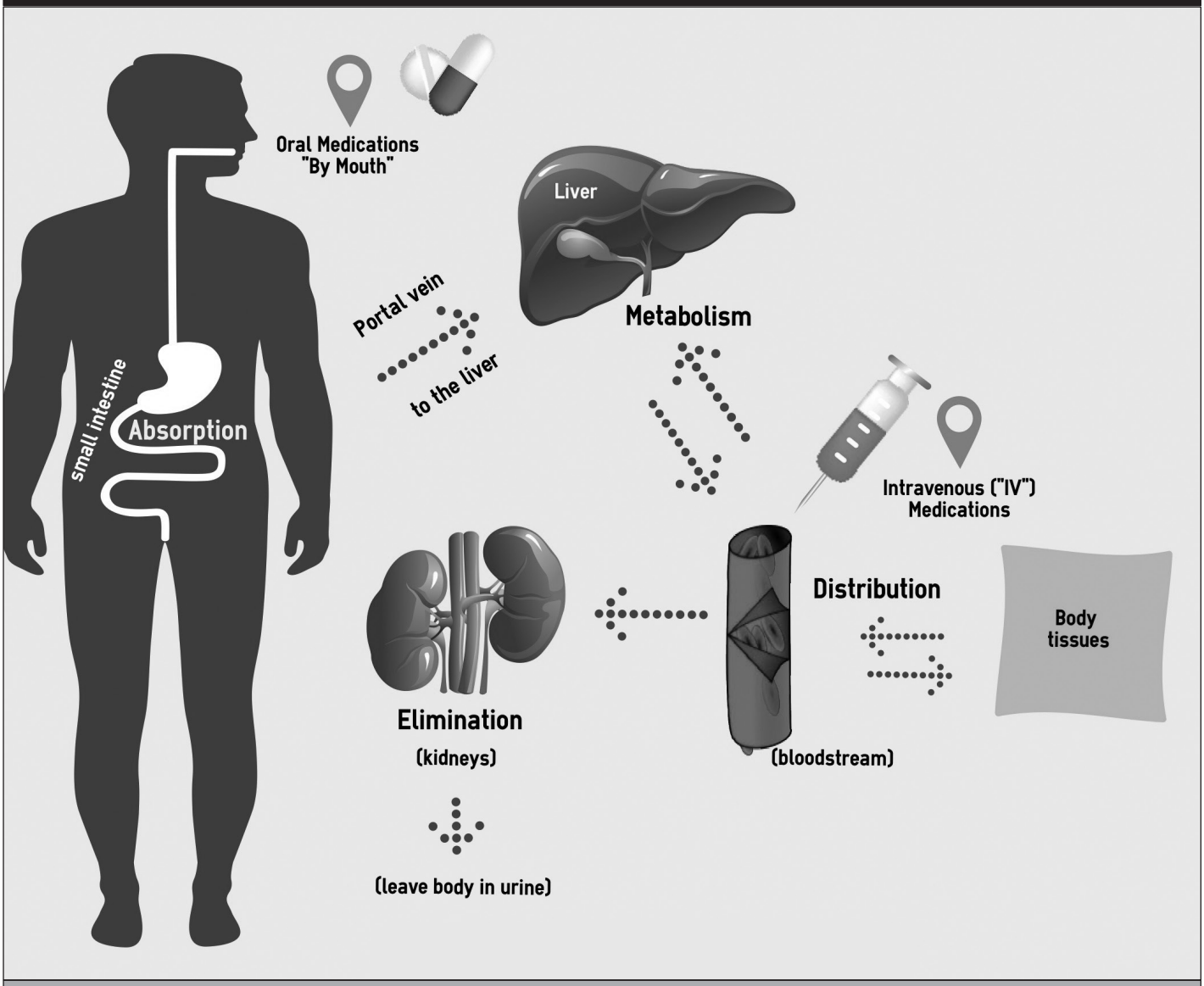
Answers on page 32.

Drug Processing: The Basics

In order to understand drug processing in any person, regardless of age, a few key terms must be reviewed. Drug processing by the body, known as pharmacokinetics, consists of four key stages: **absorption**, **distribution**, **metabolism**, and **elimination**. Drug absorption refers to a process by which a medication reaches the bloodstream after it is administered to the patient.[24] Drugs can be administered in several different ways: by mouth ("orally"); by placing under the tongue ("sublingually"); by placing in the cheek ("buccally"); by injection into a vein ("intravenously") or into a muscle ("intramuscularly") or just beneath the skin ("subcutaneously"); by insertion into the eye ("ocular route") or the ear ("otic route") or the rectum ("rectally") or the vagina ("vaginally"); and by application on the skin ("topically") or through the skin using a patch ("transdermal route"). Medications can also be delivered by inhalers or nebulizers into the lung or even sprayed into the nose. The oral route is often the safest and most convenient way to deliver medications, and therefore, this route will be used to explain all four stages of drug processing **(Figure 1).**

When given orally, absorption of most medications occurs in the small intestine (although some medications may start being absorbed in the mouth or the stomach). After moving through the wall of the intestine, the drug will then pass through the liver where some of the medication may be chemically broken down by liver cells. This phenomenon is called the **first-pass effect**, and for some oral medications, this process can drastically reduce the amount of drug that is available for use by the patient's body. This effect only occurs for oral medications and not

Figure 1. Four Stages of Drug Processing



Infographic created using Easel.ly and printed with permission from Laura Meyer-Junco.

those delivered by injection, patch, inhaler, or sublingual dosage forms. This also explains why medication doses for the same drug may be lower when given by injection than when given orally by mouth.

After a drug is absorbed, it becomes available to the bloodstream and can distribute to the body's tissues, where the medication can exert its effect. Drug distribution is the movement of a drug from the bloodstream to the body's tissues.[24] Where and how drugs distribute often depends on whether the drugs dissolve in water (referred to as **water-soluble**) or dissolve in fat (known as **fat-soluble**). Fat-soluble medications tend to distribute very quickly into tissues, like the brain, and can build up and linger in fatty tissues, which can cause drug effects to last longer. The amount of protein in the blood can also affect drug distribution. Some medications will be become bound by proteins circulating in the blood and therefore, be less available to exert their effects in the tissues.[24,25,26,27]

As mentioned previously, some drugs are partially broken down in the liver before they exert their actions, but many drugs, regardless of their route of administration, are metabolized after they act in the tissues. Drug metab-

olism is the "chemical alteration of a drug by the body," and it primarily takes place in the liver.[24] Metabolism in the liver occurs by two different mechanisms, called **Phase I** and **Phase II metabolism**. Phase I metabolism relies on enzymes produced in liver cells (called cytochrome P-450 or CYP enzymes), whereas Phase II does not. The purpose of metabolism is to convert a drug from its original form to a different product called a **metabolite**. Metabolites can be active—meaning still can exert an effect on the body—or inactive—meaning having no activity. Metabolites then can be eliminated or removed from the body by excretion into the urine or feces.

Elimination is the "removal of drugs from the body," and all drugs undergo this final process.[24] Most drugs are eliminated through the kidneys into the urine, and therefore, kidney function must be considered when dosing many medications. Some drugs, however, are eliminated by excretion into bile, which is a greenish yellow fluid produced by the liver.[24] After leaving the liver, bile enters the digestive tract to be excreted in the feces.

Age-Related Changes in the Older Adult and Important Drug Safety Considerations

Understanding age-related changes in drug processing (or pharmacokinetics) and drug response (or pharmacodynamics) is crucial to safe use of medications in the elderly population. Clinical experience and research have demonstrated that the same dose of a given drug administered to a younger patient can produce a much different response when given to an older adult of the same sex and comparable bodyweight.[25] Altered medication sensitivity and age-related changes in drug processing such as absorption, distribution, metabolism, and elimination may be responsible for this clinical phenomenon. In the following sections, changes in drug processing at every stage will be discussed in addition to a review of age-related changes in medication sensitivity.

Age-Related Changes In Absorption: The Route of Administration Is Important

Oral medications are absorbed via the gastrointestinal (GI) tract—the organ system containing the stomach, small intestine, and large intestine. Age-related changes in the GI tract can include lower acidity in the stomach, slower emptying of the stomach into the small intestine, sluggish transit time through the GI tract, decreased secretions, and decreased blood flow to the intestines.[2, 25,26,27] About 5-10% of older adults have decreased acid secretion in the stomach due to age alone, but widespread use of acid-suppressive therapy including proton-pump inhibitors such as omeprazole (Prilosec) and pantoprazole (Protonix) and histamine-2 blocker medications such as ranitidine (Zantac) and famotidine (Pepcid) may contribute to a greater percentage of older adults experiencing reduced stomach acidity.[27,28] Lower stomach acidity can lead to reduced absorption and thus reduced efficacy of medications that require an acidic environment to be absorbed. Medications that require stomach acid for absorption include certain agents used to treat fungus infections such as itraconazole (Sporanox, Onmel) and ketoconazole (only generic), and other medications such as calcium carbonate and iron supplements. Older adults taking calcium for bone health and also taking an acid suppressing medication should be counseled by the pharmacist to either take calcium with meals or switch to a calcium citrate product to increase absorption. With the high number of falls and fractures occurring annually among older adults, calcium product selection to improve bone health is an important safety consideration.

It is also important to consider the impact of delayed stomach emptying on the rate of oral medication absorption in the older adult. Delayed stomach emptying may be a natural part of aging, but it can also occur in older adults due to certain conditions such as diabetes and Parkinson's disease or after certain surgical procedures. Since most oral medications are absorbed in the small intestine, sluggish stomach emptying could delay the time it takes for an oral medication to be absorbed and then exert its effect in the body. For example, first doses of oral pain medications may take longer to be absorbed in the older adult, and therefore, adequate time should be allowed for response before administering another dose.[29,30] Slowing of GI transit time may also prolong the effects of **extended release medications**, including long-acting opioid medications for pain, and thus, if side effects did occur, harm to the patient could persist for much longer than anticipated.[29] Therefore, it may be prudent to try short-acting medications with shorter durations of effect first to ensure tolerability and safety before starting the medication in a longer acting dosage form. With delayed stomach emptying, certain medications may also spend more time in contact with the mucosal lining in the stomach, which may increase the risk for ulcer formation with medications such as ibuprofen (Motrin, Advil) and bone

modifying agents for low bone mass or osteoporosis such as alendronate (Fosamax), risedronate (Actonel), and ibandronate (Boniva).[31]

Older adults may also experience trouble swallowing due to a decrease in saliva, dry mouth from certain medications, or due to various diseases such as dementia or Parkinson's disease. Medications that can be taken sublingually—under the tongue—or are available in liquid form may be preferred in these patients. Certain medications can also be crushed and placed in soft food; however, it is important to remember that **enteric-coated** tablets such as enteric-coated aspirin as well as extended-release medications like long-acting pain medications or long-acting blood pressure medications should not be crushed. Enteric-coated medications are designed to avoid dissolving in the stomach. If these medications were crushed, the coating would be broken resulting in a rapid release of the medication and potential irritation of the stomach lining. Extended-release medications are formulated to last longer than regular-release medications. The abbreviations ER or XR or XL or XT (extended-release), LA (long-acting), SR (sustained release), SA (sustained action) CR (controlled release), and CD (controlled delivery) indicate that a medication is an extended-release formulation. Extended-release medications should not be crushed or split because doing so would destroy the slow release design of the medication and lead to a rapid development of toxicity. One exception is metoprolol extended-release (Toprol XL) tablets, which are scored and may be split in half.

In the older adult, absorption from other routes of administration outside of the GI tract may also be altered compared to younger patients. For instance, potential age-related changes in the skin could affect absorption from transdermal patches. With age, blood flow to the skin may be reduced, and skin can be drier and thinner. In older patients with advanced disease such as cancer, there can also be a loss of fatty tissue under the skin. All of these changes can potentially reduce the absorption of fat-soluble medication from transdermal patches, such as fentanyl, testosterone, and estradiol.[26] Although the data on fentanyl (Duragesic) pain patches in patients with reduced subcutaneous fatty tissue is limited, clinical experience suggests that patients with minimal body fat may absorb less drug from the fentanyl patch, and therefore, have a reduced response.[32] The danger occurs when patch doses are increased aggressively due to lack of response and then subsequently changed to what is deemed to be an equivalent dose of an oral pain medication. This can lead to overdose and harm to the patient. Heat should also never be applied to fentanyl patches in an effort to increase the absorption of the medication through the skin. Heat from a heating pad or blanket, hot bath water, or even a fever can cause greater release of drug from fentanyl pain patches and lead to adverse drug effects such as sedation and difficulty breathing. Lastly, all patches used by the older adult—whether for pain, blood pressure, or smoking cessation—should be accounted for on a daily basis to ensure that extra patches are not applied inadvertently, which could lead to adverse drug events.[32]

Although important considerations exist for administering medications through the skin or GI tract in the older adult, absorption from the sublingual route—under the tongue—and the buccal route—via the cheek—is well preserved in these patients.[26] Medications that are administered under the tongue such as sublingual nitroglycerin are absorbed in the mucosa in the mouth and quickly enter the bloodstream, effectively bypassing the GI tract entirely. Pharmacists should counsel patients, regardless of age, to place nitroglycerin under the tongue and never swallow it. If nitroglycerin were to be taken orally, it would end up passing through the gut wall and into the liver, where it would be degraded completely and thus be unavailable for use by the body to relieve chest pain.

Age-Related Changes in Distribution: The Importance of Body Fat, Water, and Skeletal Muscle

Changes in body composition occur as a person ages, and these alterations can affect where and how certain drugs distribute into the body's tissues. Body fat in the older adult can be increased by 25% to 30% with an associated decrease in muscle mass by 25% to 30%.[26] Keep in mind that this ratio of body fat to lean muscle mass is often more exaggerated in older female patients.[33] The older adult's total body water, regardless of gender, is also decreased, potentially by 10-15% (see **Table 3, *page 10***).[27] These changes can affect the distribution of fat-soluble and water-soluble medications in the older adult and lead to adverse drug events if medications are not judiciously prescribed. The increase in body fat is clinically very important because it can cause many fat-soluble psychotropic medications to accumulate in fatty tissue leading to excess sedation, drowsiness, confusion, and falls.[34] When

Table 3. Age-Related Changes in Drug Processing ("Pharmacokinetics")[25,26,27,28]

Step in Drug Processing	Changes in Older Adults	Effect on Medications
Absorption		
Stomach acid	Potentially decreased	Reduced absorption of iron, calcium, and certain anti-fungal medications.
Movement through the gastrointestinal (GI) tract	May be decreased with slower stomach emptying	-May prolong effects of extended-release medication. -Allows more contact time in stomach for NSAIDs, increasing ulcer risk.
Saliva and intestinal secretions	May be decreased	-Difficulty swallowing some medications. -Some medications (such as anticholinergics) may worsen dry mouth.
Distribution		
Body fat	Increased	Fat-soluble medications may accumulate in fatty tissue (higher risk for adverse effects).
Body water	Decreased	Water-soluble medications can reach high levels in blood (higher risk for adverse effects).
Protein in the blood	Unchanged or decreased in frail or malnourished patients	Greater risk for adverse effects from highly protein bound drugs **(Table 4).**
Metabolism		
Blood flow to the liver	Decreased	Reduces first-pass effect through the liver. May lead to increased blood levels of certain oral medications.
Liver size	Decreased	-Uncertain what effect, if any, this change has on drug metabolism. -Use medications undergoing phase I metabolism with caution **(Table 5).**
Elimination		
Kidney size	Decreased	-Reduced ability of the kidney to remove drugs and metabolites from the body. -Dose reduction required for many medications.
Blood flow to the kidney	Decreased	
NSAIDs = nonsteroidal anti-inflammatory drugs		

fat-soluble drugs accumulate in fatty tissue, adverse effects can linger longer because these medications will take longer to be cleared from the body.[26,27] Examples of fat-soluble drugs that pose such a problem to older adults include psychotropic medications like diazepam (Valium) and chlordiazepoxide (Librium) for anxiety, haloperidol (Haldol) for psychosis or delirium, desipramine (Norpramin) for depression or nerve pain, and prochlorperazine (Compazine) or promethazine (Phenergan) for nausea and vomiting.[2,26,27,33] If alternative medications are not available and such fat-soluble medications are to be used, lower doses and less frequent dosing should be implemented.[27]

Due to lower total body water, water-soluble medications should also be used cautiously in the older adult. With decreased body water, water-soluble medications are capable of achieving high levels in the blood. With higher blood levels, there is a greater potential for side effects and adverse drug events to occur.[26,33] To visualize this, picture dissolving an ounce of red dye in two different containers: the first container is a gallon of water and the second container is a half-gallon of water. The gallon of water will appear light pink, but the half-gallon will have a much darker pink color due to a higher concentration of the red dye in a smaller volume of water.[33] A similar concept occurs when an older adult is given a water-soluble medication in the same dose as a younger patient. The older adult would be expected to have much higher blood levels and therefore, be at risk for toxic drug effects.[27] When water-soluble drugs are used in the older adult, lower doses should be prescribed. Examples of common water-soluble medications include morphine (MS Contin, Avinza, Kadian) for pain, the beta-blocker atenolol (Tenormin) for blood pressure, and aminoglycoside antibiotics such as gentamicin (Garamycin) for bacterial infections.[2,27,28] Alcohol is also a water-soluble substance, and due to lower total body water, older adults may experience higher blood levels of alcohol than younger adults for the same amount of alcohol ingested.[2] Therefore, older adults should be advised to avoid or limit alcohol consumption, especially with a history of falls or when taking medications that also act on the central nervous system. A similar strategy of using lower doses should be implemented when medications that distribute into lean muscle mass are prescribed for the older adult. Like total body water, older adults also have reduced muscle mass, and therefore, medications that distribute into lean muscle like the heart medication digoxin (Digitek, Digox, Lanoxin) should be used in lower doses.[26,27]

In the healthy older adult, the amount of protein in the body is usually unchanged but can be significantly reduced in patients who are frail or malnourished.[26,27] Some common diseases can also result in lower levels of protein in the body including heart failure, kidney failure, cirrhosis of the liver, and some cancers.[2] Many medications bind to proteins in the blood, and if there is less protein present to bind the drug, more unbound drug is available. In the body, unbound drug is the portion of the drug capable of reaching target tissues in the body and exerting its action. If less protein is available in the blood to bind drugs as in some older adults, there is a greater risk for adverse drug effects at standard drug doses.[2,25,26,33,35] Examples of medications that are highly protein bound are shown in **Table 4.** Medications in this table, particularly the blood thinner warfarin (Coumadin), should be dosed cautiously with a "start low and go slow" approach in older adults, especially if protein deficiency is present. There is also a higher risk for drug-drug interactions if two or more highly protein bound medications are used at the same time. For instance, concurrent use of other protein bound medications (**Table 4**) could dislodge warfarin from its protein binding sites and cause higher warfarin levels in the body. This could result in greater blood thinning and thus, the potential for bleeding, bruising, and other complications.

Table 4. Highly Protein-Bound Medications[26,27,28,33,35]

Acetazolamide (Diamox)
Amiodarone (Cordarone, Pacerone)
Amitriptyline (Elavil)
Ceftriaxone (Rocephin)
Diazepam (Valium)
Fentanyl (Duragesic, Actiq, Fentora, Abstral)
Flurazepam (Dalmane)
Furosemide (Lasix)
Haloperidol (Haldol)
Ibuprofen (Advil, Motrin)
Indomethacin (Indocin)
Ketoconazole (generic only)
Lorazepam (Ativan)
Methadone (Dolophine)
Midazolam (Versed)
Naproxen (Aleve, Naprosyn, Anaprox)
Phenytoin (Dilantin)
Prazosin (Minipress)
Propofol (Diprivan)
Salicylates (such as aspirin)
Valproate (Depacon, Depakene, Depakote)
Verapamil (Verelan, Calan, Isoptin, Covera-HS)
Warfarin (Coumadin)
This list provides examples of highly-protein bound medications but is not all inclusive.

Age Related Changes in Metabolism: What Happens in the Liver?

In all patients, the metabolism or break down of medications occurs primarily in the liver. In the older adult, however, the size of the liver can be decreased by 20% to 40%, and blood flow to the liver can be reduced by 35% to 40%.[26,28] For medications taken by mouth, this can mean that less drug will be broken down during its first-pass through the liver. Medications like oral morphine (MS Contin, Avinza, Kadian) and codeine-containing products for pain or propranolol (Inderal) and verapamil (Calan) for blood pressure may reach higher blood levels in the older adult. For these medications, doses should be reduced because standard doses may cause adverse drug effects.[26,27] It is uncertain what effect, if any, age has on CYP enzymes and thus Phase I metabolism in the liver cells. However, research has shown that anxiety medications undergoing Phase I metabolism such as diazepam (Valium) and alprazolam (Xanax) may result in greater risk of hip fracture in older adults compared to anxiety medications such as lorazepam (Ativan) and temazepam (Restoril) that are not metabolized in this way.[36] This suggests that older adults, particularly frail or sick older adults, may have some reduced CYP enzyme function in the liver.[37] For this reason, medications that are extensively broken down by the CYP enzymes produced by liver cells should be used with a degree of caution; medication doses should be started low and slowly increased. See **Table 5** for a list of common medications that are metabolized by Phase I CYP enzymes.[2,13,38,39,40,41,42] It is also important to note that if a patient takes multiple medications that undergo Phase I metabolism, there is the potential for drug-drug interactions and toxic effects of these medications. This can occur as medications compete for metabolism by a limited number of CYP enzymes. Certain medications can also inhibit various CYP enzymes, making them less capable of metabolizing medications and thereby increasing toxicity. For instance, if drug A inhibits or blocks the function of the CYP3A4 enzyme, higher levels of drug B will occur in the body if drug B is ordinarily metabolized by this liver enzyme. With polypharmacy common among older adults, the potential for drug-drug interaction is high, and prescribers and pharmacists should routinely screen for such interactions in order to prevent or avoid adverse drug events.

In the setting of advanced liver disease such as alcoholic liver disease or cirrhosis, it is important to point out that Phase I metabolism will be impaired, regardless of how old a patient is. Therefore, the medications shown in **Table 5** should be avoided in patients with overt diagnosed liver disease due to the potential for increased side effects.[42] Phase II metabolism, on the other hand, does not require the use of CYP enzymes, and thus, it is thought to be preserved in patients with liver disease and those with advanced age. Therefore, medications that undergo Phase II metabolism are thought to be potentially safer and require less dose adjustment in the older adult.[26,27] For example, lorazepam (Ativan) undergoes Phase II metabolism and is considered safer than diazepam (Valium), which undergoes Phase I metabolism.

Age-Related Changes in Elimination: The Impact of Reduced Kidney Function on Drug Dosing

While age-related changes in liver function are not as well understood, changes in kidney function as one ages have been well described. With age, the size of the kidney becomes smaller and can be decreased by up to 25%.[25,26,27,28] Blood flow to the kidney is also reduced, up to almost 50%, in older adults.[25] Both of these changes can impair the ability of the kidney to filter and excrete drugs and metabolites from the body. The most common estimate of how well the kidneys are filtering and excreting drugs is called the **creatinine clearance (CrCl)** calculation. Studies suggest that after the age of 20 years, the kidney's creatinine clearance decreases by 1% per year.[27] Assuming a person has a CrCl of 120 ml/min at the age of 20 years, the same person at the age of 80 years would have at best a CrCl of 60 ml/min. Some older adults may experience even further reductions in their kidney function due to the presence of chronic conditions such as diabetes, heart failure, or long-standing hypertension. Determining a patient's kidney function is important because if medications are not appropriately adjusted for kidney impairment, toxicity of medications can occur rapidly and may be prolonged. For instance, morphine (MS Contin, Avinza, Kadian) is metabolized in the liver to the metabolite morphine-6-glucuronide (M6G), which can cause sedation and hallucinations if not adequately cleared from the body. To be cleared from the body, this metabolite must be excreted through the kidney. Therefore, if kidney function is impaired or reduced as in many older adults, side effects from morphine's metabolites may be prolonged. Medications such as morphine must be reduced in the setting of decreased kidney function

Table 5. Medications Metabolized by Phase I CYP Enzymes and Medications That Inhibit CYP Enzymes[2,13,38,39,40,41,42]

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Amitriptyline (Elavil) Acetaminophen (Tylenol) Cyclobenzaprine (Flexeril) Duloxetine (Cymbalta) Haloperidol (Haldol) Imipramine (Tofranil) Methadone (Dolophine) Naproxen (Aleve, Naprosyn) Nortriptyline (Pamelor) Olanzapine (Zyprexa) Ondansetron (Zofran) Verapamil (Verelan, Calan, Isoptin, Covera) Warfarin (Coumadin)	Celecoxib (Celebrex) Diclofenac (Voltaren, Zorvolex, Cataflam) Fluoxetine (Prozac) Glimepiride (Amaryl) Glipizide (Glucotrol) Glyburide (Diabeta, Glynase) Ibuprofen (Motrin, Advil) Irbesartan (Avapro) Losartan (Cozaar) Naproxen (Aleve, Naprosyn) Phenytoin (Dilantin) Sulfamethoxazole (Bactrim) Torsemide (Demadex) Warfarin (Coumadin)	Amitriptyline (Elavil) Carisoprodol (Soma) Clopidogrel (Plavix) Citalopram (Celexa) Diazepam (Valium) Esomeprazole* (Nexium) Lansoprazole* (Prevacid) Omeprazole* (Prilosec) Pantoprazole* (Protonix) Phenytoin (Dilantin) Warfarin (Coumadin)	Amitriptyline (Elavil) Aripiprazole (Abilify) Carvedilol (Coreg) Codeine Desipramine (Norpramin) Donepezil (Aricept) Duloxetine* (Cymbalta) Flecainide (Tambocor) Fluoxetine* (Prozac) Haloperidol* (Haldol) Hydrocodone Imipramine (Tofranil) Metoclopramide* (Reglan) Methadone* (Dolophine) Metoprolol (Lopressor, Toprol XL) Nortriptyline (Pamelor) Ondansetron (Zofran) Oxycodone (OxyContin, Roxicodone) Paroxetine (Paxil) Risperidone (Risperdal) Tamoxifen (Soltamox) Tramadol (Ultram) Venlafaxine (Effexor)	Alprazolam (Xanax) Amitriptyline (Elavil) Apixaban (Eliquis) Amiodarone (Cordarone, Pacerone) Amlodipine (Norvasc) Aripiprazole (Abilify) Atorvastatin (Lipitor) Clarithromycin* (Biaxin) Diazepam (Valium) Diltiazem (Cardizem, Cartia, Taztia)* Fentanyl (Duragesic) Fluoxetine (Prozac)* Haloperidol (Haldol) Lovastatin (Mevacor, Altoprev) Methadone (Dolophine) Midazolam (Versed) Quetiapine (Seroquel) Simvastatin (Zocor) Solifenacin (Vesicare) Trazodone (Oleptro) Rivaroxaban (Xarelto) Verapamil (Verelan, Calan, Isoptin, Covera) Zaleplon (Sonata) Zolpidem (Ambien) Warfarin (Coumadin)
Inhibitors	***Inhibitors***	***Inhibitors***	***Inhibitors***	***Inhibitors***
Amiodarone (Cordarone, Pacerone) Ciprofloxacin (Cipro) Fluvoxamine (Luvox)	Amiodarone (Cordarone, Pacerone) Fenofibrate (Lofibra, Lipofen, Tricor) Fluconazole (Diflucan) Fluvoxamine (Luvox) Sertaline (Zoloft)	Fluoxetine (Prozac) Fluvoxamine (Luvox) Proton Pump Inhibitors Medications above indicated by *	Amiodarone (Cordarone, Pacerone) Bupropion (Wellbutrin, Budeprion, Zyban) Sertraline (Zoloft) Medications above indicated by *	Amiodarone (Cordarone, Pacerone) Ciprofloxacin (Cipro) Fluconazole (Diflucan) Grapefruit juice Medications above indicated by *

This medication list is not all inclusive. The medications selected above represent medications commonly prescribed for older patients or those that are frequently implicated in serious drug-drug interactions.

to avoid excess side effects and toxicity. Fortunately, the manufacturers of medications provide pharmacists and prescribers with dose adjustments of medications based on a patient's creatinine clearance. However, it is often difficult to accurately calculate the creatinine clearance in an older adult because the key factor used in this calculation is produced by muscle in the body. As discussed previously, older adults often have reduced muscle mass, and therefore, this factor known as serum creatinine may not be a reliable indicator of kidney function in an aging patient. It is critically important to use appropriate discretion when dosing medications that rely on the kidneys for removal from the body, especially in the older adult.

In addition, several medications can also worsen kidney function in the older adult and should either be avoided or used with caution. These include medications such as nonsteroidal anti-inflammatory drugs (NSAIDs)—ibuprofen (Advil, Motrin), naproxen (Aleve, Naproysn), ketorolac (Toradol), indomethacin (Indocin), celecoxib (Celebrex)—and blood pressure medications such as lisinopril (Prinivil, Zestril), enalapril (Vasotec), captopril (Capoten), valsartan (Diovan), losartan (Cozaar), and candesartan (Atacand). Water pills such as furosemide (Lasix) and hydrochlorothiazide (Microzide) and certain antibiotics like gentamicin (Garamycin) can also worsen kidney function, and should be used carefully in the older adult.

Test Your Knowledge #2

Since Mrs. Smith is 86 years old, Dr. Potter should anticipate age-related changes in absorption, distribution, metabolism, and elimination. Which of the following statements is true?

1. Body fat increases in older age and may increase the risk of toxicity from fat-soluble medications.
2. Body water increases in older age and may increase the risk of toxicity from water-soluble medications.

Answers on page 32.

Age-Related Changes in Drug Sensitivity: Pharmacodynamics

Separate from changes in drug processing, older adults may also experience increased or decreased sensitivity to certain medications due to changes in their cardiovascular system, which is composed of the heart, veins, and arteries and the central nervous system which includes the brain, spinal cord, and nerves. Age-related changes in medication sensitivity or pharmacodynamic changes increase the complexity of medication use in older adults, and therefore, cautious dosing and careful monitoring of medication response is critically important in the older adult.[26] In the next few sections, age-related changes in the cardiovascular and central nervous systems will be reviewed, and recommendations for safe and effective use of medications will be provided.

Aging and the Cardiovascular System

As people age, the arteries and other vasculature can stiffen and become less capable of absorbing the impact of high pressure from the beating heart.[27] As a result, older adults often develop isolated systolic hypertension, or high systolic (the top number in a blood pressure reading) blood pressure. This effect, as well as other cardiovascular changes, make the older adult more prone to decreases in blood pressure upon standing. This phenomenon known as **orthostatic hypotension** increases with age and has been found to occur in greater than 30% of community dwelling patients over the age of 75 years and up to 50% of nursing home residents.[43] By definition, orthostatic hypotension is a reduction in systolic blood pressure of 20 mmHg or more or a reduction in diastolic (the bottom number in a blood pressure reading) blood pressure of at least 10 mmHg within three minutes of standing.[43] When all people, regardless of age, stand up from a sitting or lying position, gravity causes blood to pool in the lower half of the body, dropping blood pressure and reducing the amount of blood available for the heart to pump to the brain. In the younger, healthy adult, however, the body quickly responds to this short drop in blood pressure by accelerating the heart rate and constricting blood vessels. This returns blood pressure to normal before symptoms such as dizziness and lightheadedness can develop.[44] When the older adult gets up from a seated position, the heart rate response is diminished so the body is unable to compensate for the drop in blood pressure as well as a younger adult. Therefore, the older adult may develop symptoms from the orthostatic

hypotension such as dizziness, lightheadedness, weakness, visual changes, confusion, and temporary loss of consciousness which is known as syncope.[43] All of these symptoms increase the risk of falls, and as mentioned previously, falls are a common cause of injury, fracture, hospitalization, and even death in the older adult population.[10,11,12,13,14,15] As orthostatic hypotension increases with age and can result in great harm to the older adult, health care professionals should be able to recognize which medications may cause orthostatic hypotension in elderly patients.

Medications that are commonly implicated in orthostatic hypotension include those that lower blood pressure or those that lower heart rate thereby blunting the body's means of compensating for lower blood pressure.[43] Common cardiovascular medications causing orthostatic hypotension include the alpha blockers terazosin (Hytrin), doxazosin (Cardura), and prazosin (Minipress); vasodilators such as hydralazine (generic only) and minoxidil (Loniten); diuretics such as furosemide (Lasix), bumetanide (Bumex), and hydrochlorothiazide (Microzide); nitrates such as nitroglycerin (see **Table 2, *page 5***); and medications that lower heart rate such as clonidine (Catapres, Kapvay) or beta-blocker medications such as metoprolol (Lopressor, Toprol XL), carvedilol (Coreg), and atenolol (Tenormin).[27,43] Other non-cardiovascular medications that can cause orthostatic hypotension include tricyclic antidepressants such as amitriptyline (Elavil), desipramine (Norpramin), and nortriptyline (Pamelor); nausea medications such as prochlorperazine (Compazine) and promethazine (Phenergan); and antipsychotic medications including olanzapine (Zyprexa), quetiapine (Seroquel), and risperidone (Risperdal).[13] Medications used for Parkinson's disease or restless legs syndrome (see **Table 2, *page 5***), skeletal muscle relaxants such as tizanidine (Zanaflex), sedatives such as temazepam (Restoril), opioid pain medications (particularly morphine—MS Contin, Avinza, Kadian), and alcohol can also cause or worsen orthostasis.[27,31,45] Common conditions in the older adult can also precipitate sudden orthostatic hypotension including dehydration, diarrhea, vomiting, fever, hemorrhage, and heart attack. Patients with diabetes, Parkinson's disease, heart failure, and Lewy Body dementia may also have chronic orthostatic hypotension.[43] Medications known to cause orthostatic hypotension should be used with caution or not at all in older adults, especially in those with a history of falls or other conditions that predispose them to orthostatic hypotension as mentioned above.

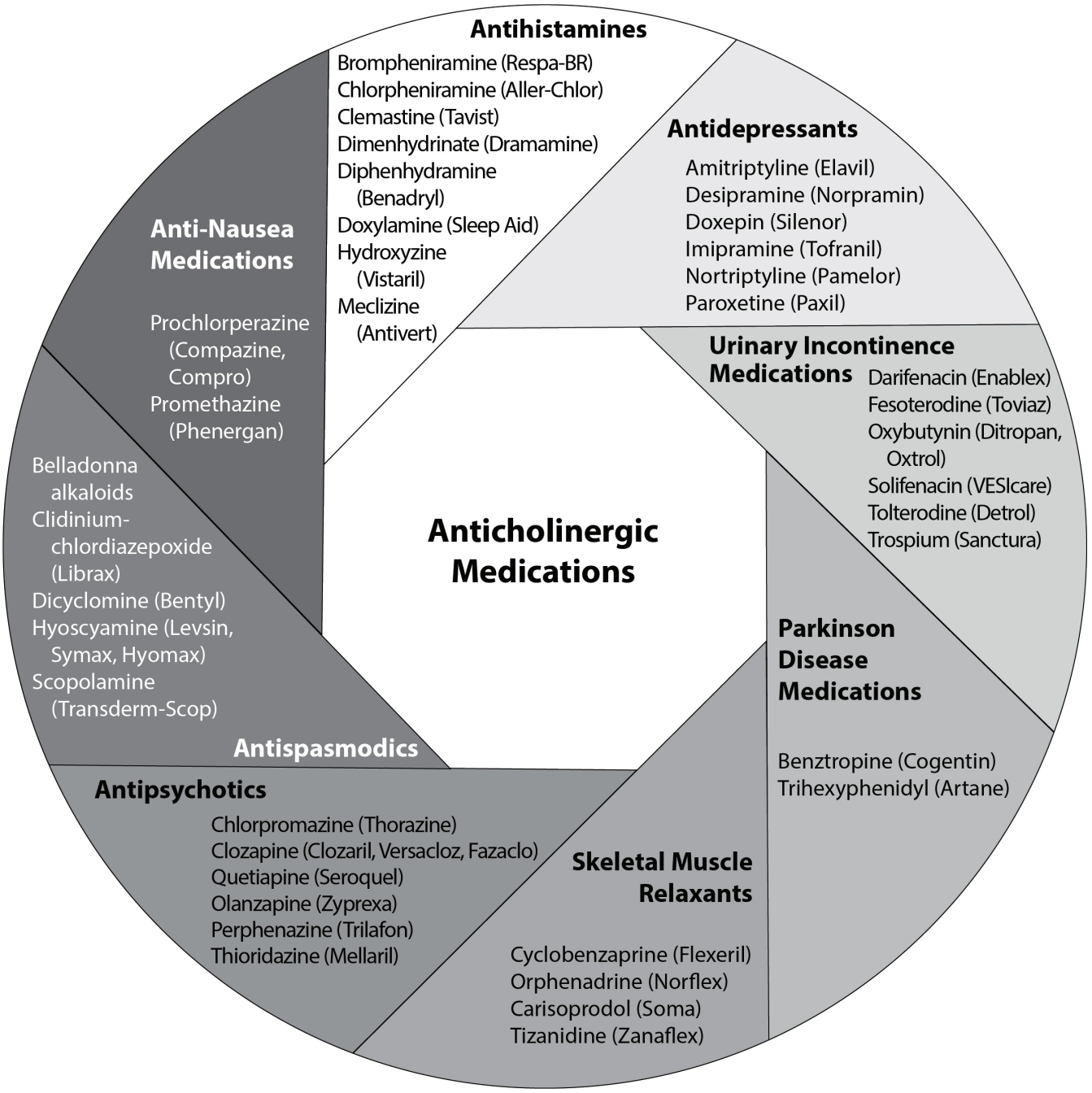
Aging and the Central Nervous System

Age-related changes occur in the central nervous system, particularly in the brain. As one ages, the number of neurons and receptors in the brain changes, with the older brain having a smaller reserve of chemical signals or neurotransmitters compared to younger brains.[26,27] The ordinarily tightly-knit blood vessel layer, known as the blood brain barrier, surrounding the brain also becomes more permeable in the older adult, allowing molecules and chemicals greater access to the older brain.[26,27] These changes together explain why older adults are more likely to experience adverse effects from psychotropic medications such as drowsiness, confusion, balance issues, and falls. Due to the increased sensitivity of the older brain to psychotropic medications, the medications listed in **Table 2 *(page 5)*** should be avoided or used only with great caution and close monitoring.

The actions of **acetylcholine**—the neurotransmitter in the brain responsible for memory, thinking, and language—may also be reduced in older adults, contributing to the cognitive (or mental) decline of normal aging.[46] Decreased actions of acetylcholine in the older brain also increases the older adult's sensitivity to medications that block the activity of acetylcholine at cholinergic neurons. These medications are said to possess strong anticholinergic properties and belong to several different medication classes as shown in **Figure 2 *(page 16)***.[19,47] With an increased permeability of the blood brain barrier and decreased reserves of acetylcholine in the brain, older adults are particularly sensitive to the effects of **anticholinergic medications** on the central nervous system. These adverse effects may include memory and thinking impairments, drowsiness, delirium, worsening dementia, restlessness, fatigue, balance issues, falls, and decreased ability to perform every day activities.[48] As acetylcholine functions in many different body systems, anticholinergic medications can also cause side effects outside of the central nervous system (i.e. peripheral system), including constipation, dry mouth, increased heart rate, dry eyes, blurred vision, and urinary retention.[48] With both central and peripheral effects, anticholinergic medications can exacerbate or worsen common conditions in the older adult including glaucoma, constipation, dementia, urinary issues due to enlarged prostate, and various heart conditions.[46]

Due to concerns over the use of anticholinergic medications and other potentially inappropriate medications in older adults, expert consensus guidelines such as the Beers Criteria and the Screening Tool of Older People's Prescriptions (STOPP) criteria have been developed.[19,20,21] These guides alert clinicians to the potential

Figure 2. Anticholinergic Medications[19,47]



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harms of potent anticholinergic medications such as the first generation antihistamines which includes diphenhydramine (Benadryl); tricyclic antidepressants such as amitriptyline (Elavil) and imipramine (Tofranil) shown in **Table 2,** ***(page 5)***; bladder control medications such as oxybutynin (Ditropan, Oxytrol); and other agents as shown in **Figure 2**. Both the Beers criteria and the STOPP criteria also warn clinicians about the potential of additive anticholinergic effects if multiple anticholinergic products are taken by an older adult at the same time.[19,20,21] It is important to recognize that many potent anticholinergic medications do not require a prescription

and are available over-the-counter (OTC) for purchase by older adults. Therefore, pharmacists and pharmacy technicians should be aware of the anticholinergic potential of the many OTC allergy medications, cough and cold products, and sleep aids containing the antihistamines diphenhydramine, chlorpheniramine, clemastine, dimenhydrinate, doxylamine, and meclizine. The highly anticholinergic medication, oxybutynin, is also now available as the OTC oxybutynin (Oxytrol) patch for the management of urinary incontinence due to bladder spasms in women. Pharmacy technicians may be instrumental in reducing the use of highly anticholinergic OTC products in older adults by referring older adults to the pharmacist for counseling and for alternative product selection. For example, the pharmacist may direct the older adult to an antihistamine with less anticholinergic potential and therefore less risk for sedation, if a medication is necessary for management of allergies. Non-sedating antihistamines include loratadine (Claritin, Alavert), desloratadine (Clarinex), and fexofenadine (Allegra).[46] These antihistamines are referred to as "second generation antihistamines" while the antihistamines in **Figure 2** are "first generation antihistamines."

Many other psychotropic medications can impair memory and thinking in the older adult. Older adults are particularly sensitive to a class of anti-anxiety medications known as "benzodiazepines." As shown in **Table 2** ***(page 5)***, these medications include alprazolam (Xanax), lorazepam (Ativan), diazepam (Valium), clonazepam (Klonopin), and several others. Medications in this class increase the risk for memory and thinking impairments, delirium, falls, fractures, and even motor vehicle accidents in older adults.[19] To appreciate why older adults may be particularly vulnerable to these medications, it may be helpful to review other clinical uses of benzodiazepines. Medications in this class are often used in patients undergoing procedures due to their ability to induce amnesia (memory loss).[49] Therefore, it is not hard to understand how regular, scheduled use of benzodiazepines in the older adult can impair memory, especially if metabolism of such agents is reduced as discussed previously.[49] According to both the Beers and STOPP criteria, benzodiazepines should be avoided in older adults.[19,20,21] Additionally, these medications should not be stopped abruptly due to the potential for significant withdrawal reactions.[19,20,21]

Medications used for insomnia also should be avoided in older adults as the harms of the treatment often outweigh the benefits.[19,20,21,50] Sleep aids such as eszopiclone (Lunesta), zolpidem (Ambien), and zaleplon (Sonata) can cause daytime drowsiness, memory impairments, hallucinations, depression, risk for fractures, motor vehicle accidents, and mood changes.[19,50] Although the Beers criteria and STOPP criteria recommend against the use of these agents, if a provider does prescribe for one of these agents, they should ideally not be used beyond 4 to 5 weeks.[19,20,21,50] In fact, due to the potential harms of these medications, the US Food and Drug Administration (FDA) has released several drug safety communication notices over the past few years warning prescribers and consumers about the risk of "next-morning impairment" after use of these sleep aids and the importance of lower doses in women and older adults.[51] Benzodiazepines that are prescribed as sleep aids including temazepam (Restoril), flurazepam (Dalmane), and triazolam (Halcion) can also lead to next-morning impairments (next-day drowsiness), and therefore should also be avoided in older adults.[19,20,21,50]

Other High Risk Medications

As discussed previously, four medication categories account for nearly 90% of all hospitalizations for adverse drug events.[9] Two of these categories—cardiovascular medications and central nervous system medications—were discussed above in the section on drug sensitivity or pharmacodynamics. These two categories are frequently implicated in adverse effects in older adults such as falls, sedation, and orthostasis. Blood thinning medications and blood sugar lowering medications, in particular, contribute to the majority of drug-related emergency room visits and hospitalizations among older adults.[9] Therefore, in the next sections, the risks of blood thinning and blood sugar lowering medications will be highlighted. Due to the complications that NSAIDs can cause especially in combination with blood thinning agents, a discussion of these readily available OTC products will follow.

Blood Thinning Medication: Increased Risk of Bleeding

Blood thinning medications contribute to the majority of hospitalizations due to adverse drug events in older adults.[9] Blood thinning medications such as warfarin (Coumadin), apixaban (Eliquis), dabigatran (Pradaxa), edoxaban (Savaysa), and rivaroxaban (Xarelto) are used to prevent and treat blood clots and stroke. The prevalence of stroke and blood clots increases with age, and

Test Your Knowledge #3

The medications listed below could be contributing to Mrs. Smith's recent falls. Match each medication below with the body system it affects (Hint: refer to Table 2 on page 5 and the sections "Aging and the Cardiovascular System" and "Aging and the Central Nervous System").

Medication:

____ 1. lorazepam (Ativan)
____ 2. amitriptyline (Elavil)
____ 3. amlodipine (Norvasc)
____ 4. metoprolol (Lopressor)
____ 5. oxybutynin (Ditropan)

Body System:

A. Central Nervous System
B. Cardiovascular System

Answers on page 32.

therefore, older adults are more likely to require use of blood thinning agents at one point in their lives.[52] This is challenging because not only are older adults at increased risk for blood clots and strokes, they are also at increased risk for bleeding. The first oral blood thinner developed, warfarin (Coumadin), reduces the risk of stroke in patients with atrial fibrillation (a heart rhythm disorder) by 64%, but it also increases the risk of major bleeding (bleeding in the brain or bleeding severe enough to require blood transfusion) by 46% for each decade of life over age 40 years.[53,54]

For the prevention of stroke in patients with atrial fibrillation and for the treatment of patients with blood clots, warfarin (Coumadin) must be frequently monitored with blood draws and subsequent dose adjustments in order to maintain an international normalized ratio (INR) between 2.0 and 3.0. Below an INR of 2.0, warfarin's efficacy is diminished, but above an INR of 3.0, the risk of bleeding is significantly increased. Keeping the INR in this narrow therapeutic window can be difficult in older adults due to the many factors that can affect the INR: vitamin K containing foods (such as green, leafy vegetables—broccoli, brussel sprouts, lettuce, cabbage, and many others), drug-drug interactions, decreased appetite, diarrhea, and multiple comorbidities (such as heart failure and liver disease).[55] As older adults are often taking numerous medications, the potential for drug-drug interactions in warfarin-treated older adults is significant. Prescription medications, OTC medications (such as aspirin), as well as herbal products have the potential to interact with warfarin, and therefore, patients should be counseled to avoid purchasing nonprescription products before discussing with a pharmacist or the prescriber. It is also important to screen older adults for use of these nonprescription products, particularly herbals, as these products are widely used by older adults and often not reported to practicing healthcare professionals.[4,56,57] The addition or the discontinuation of an interacting medication (such as an antibiotic, antifungal, steroid, heart rhythm medication, and many others) should trigger a review of the patient's warfarin regimen and INR so that any necessary adjustments can be made and complications avoided.[55] Any changes in the older adult's health (vomiting, diarrhea, fever, decreased appetite), evidence of bleeding (abnormal bruising, prolonged nose bleed, blood in urine or stool) or any falls should also trigger consultation by the provider managing the warfarin (Coumadin).

Four oral blood thinners have been developed in recent years for the treatment of clots and stroke prevention, including apixaban (Eliquis), dabigatran (Pradaxa), edoxaban (Savaysa), and rivaroxaban (Xarelto). Compared to warfarin (Coumadin), these medications have fewer food and drug interactions and do not require frequent laboratory monitoring. However, these newer agents are not without risks in the older adult, especially older adults with reduced kidney function. Decreased kidney function can lead to increased blood levels of these newer blood thinners. This is most pronounced with the use of

dabigatran (Pradaxa) followed by edoxaban (Savaysa), rivaroxaban (Xarelto), and apixaban (Eliquis).[40,41,58,59] Based on clinical trials conducted on these agents, each of the newer blood thinners are at least as effective and safe as warfarin for stroke prevention and clot treatment. In these trials, GI bleeding occurred more often with dabigatran (Pradaxa)—especially in the elderly—and with rivaroxaban (Xarelto) compared to warfarin, but all newer agents had a lower risk of intracerebral hemorrhage (bleeding in the head).[40,41,58,59] Compared to warfarin, apixaban (Eliquis) had lower rates of major and fatal bleeding in both its stroke prevention and clot treatment trials.[40] Compared to warfarin, rivaroxaban (Xarelto) had decreased rates of fatal bleeding in its stroke prevention trial and decreased rates of major bleeding in its lung clot trial; whereas edoxaban (Savaysa) reduced major and fatal bleeding in its stroke prevention trial.[41,59]

Before applying the results of these trials to the care of older adults, it is important to recognize that older adults were not highly represented in these individual trials. For instance, in the stroke prevention trials, roughly 30 to 40 percent of patients taking the newer blood thinners were over the age of 75 years.[60,61,62,63,64] For the clot treatment trials, this percentage appears to be even smaller, with only about 15% of patients in the edoxaban and rivaroxaban trials over the age of 75 years.[65,66,67,68,69] To come to a conclusion about the use of these newer blood thinners in older patients, investigators have compiled and reviewed the results of all the stroke and clot trials together.[70] Their findings suggest that the new blood thinners did not cause more bleeding in older study participants over the age of 75 years compared to younger study participants.[70] These older study participants, however, are more likely to be healthier patients and not representative of all older adults, especially older adults with frailty, multiple comorbidities, and poor kidney function.[70] Patients with poor kidney function (CrCl less than 30 ml/min), in particular, were not eligible for participation in the stroke and clot trials for dabigatran, edoxaban, and rivaroxaban.[61,62,64,65,66,67,68] In the apixaban trials, patients with a CrCl less than 25 ml/min were excluded.[63,69] Despite these trial eligibility requirements, the FDA did approve the use of these agents for stroke prevention in patients with kidney impairment below the studied cutoff. For instance, the FDA has approved the use of dabigatran 75 mg twice daily, edoxaban 30 mg daily, and rivaroxaban 15 mg daily for stroke prevention in patients with atrial fibrillation and a CrCl between 15 and 30 ml/min.[41,58,59] Due to the risks and uncertainties surrounding use of these newer agents in poor kidney function, especially in older adults, the American Geriatrics Society advises clinicians in the 2015 Beers criteria to adhere to the clinical trial eligibility criteria, and avoid use of dabigatran, edoxaban, and rivaroxaban in patients with a CrCl less than 30 ml/min.[19] The Beers criteria also states that apixaban should be avoided in patients with a CrCl less than 25 ml/min. In patients with severe or end stage kidney disease, warfarin remains the blood thinner of choice for treatment of clot conditions and prevention of stroke in atrial fibrillation according to the American College of Cardiology and the American Heart Association.[71] Selection of the most appropriate blood thinner in an older adult requires careful consideration of kidney and liver function and other factors, including cost, drug interactions, adherence (taking the medication as prescribed), history of GI bleeding, cognitive ability, and patient preference.

Due to concerns over bleeding, blood thinners are under-prescribed for older adult patients despite the increased risk for stroke with advanced age. Fear of falling is often a key factor in whether a clinician prescribes a blood thinner for an older adult.[72] The perception is that falling will increase the risk of a serious head bleed. Interestingly, a study has proposed that if a patient has a high risk of stroke, he or she would have to fall more than 295 times a year before the risk of a head bleed would surpass the patient's stroke risk.[73] In order to make an informed decision about whether to use a blood thinner for stroke prevention in older adults, clinicians should evaluate the patient's risk for stroke using validated tools and also thoroughly assess the patient's risk for bleeding.[71] Several factors may increase the older adult's risk of bleeding including high blood pressure, poor kidney or liver function, history of stroke or bleeding, alcohol use, and use of medications that also increase risk of bleeding such as aspirin, clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), and NSAIDs.[74] The patient's preference and values as well as life expectancy and individual goals should also be incorporated in the decision to initiate or discontinue blood thinning therapy in older adults.

Case 2

Mr. Baker is a 78-year-old resident of a nursing home. Over the past week, he has been complaining of dizziness and lightheadedness every morning when he gets out of bed to go to the bathroom. This morning, his nurse took his blood pressure when he was sitting and three minutes later when he was standing. The nurse discovered that Mr. Baker's systolic blood pressure decreased by 30 mmHg when he stood up this morning. The nurse is concerned that Mr. Baker's medications may be contributing to his symptoms, and she contacts the pharmacist. Mr. Baker is taking the following medications:

Apixaban (Eliquis) 5 mg by mouth twice daily for stroke prevention

Terazosin (Hytrin) 2 mg by mouth daily for his enlarged prostate and for high blood pressure

Furosemide (Lasix) 40 mg by mouth daily for swelling in his lower legs

Meclizine (Antivert) 25 mg by mouth three times daily as needed for dizziness

Paroxetine (Paxil) 20 mg daily by mouth for depression

Omeprazole (Prilosec) 20 mg daily by mouth for acid reflux

Ibuprofen (Advil) 200 mg by mouth three times daily for arthritis pain

Quetiapine (Seroquel) 25 mg by mouth daily at night for agitation

Test Your Knowledge #4

Mr. Baker is experiencing orthostatic hypotension. Which medications may be contributing to this phenomenon? Put an "X" next to the medications that apply.

____ aspirin
____ meclizine
____ terazosin
____ furosemide
____ quetiapine

Answers on page 32.

Test Your Knowledge #5

Mr. Baker is also complaining of constipation, dry mouth, and is frequently drowsy during the day. The pharmacist believes that anticholinergic medications are likely contributing to these three symptoms. Which of Mr. Baker's medications are anticholinergic? Select all that apply by marking an "X" next to the medication. (Hint: Refer to Figure 2, on page 16).

____ terazosin
____ meclizine
____ ibuprofen
____ paroxetine
____ omeprazole

Answers on page 32.

Test Your Knowledge #6

Mr. Baker is taking a blood thinner for stroke prevention. Match the following blood thinners (on the left) with the correct brand name (on the right).

____ 1. apixaban	A. Coumadin
____ 2. dabigatran	B. Xarelto
____ 3. rivaroxaban	C. Savaysa
____ 4. edoxaban	D. Eliquis
____ 5. warfarin	E. Pradaxa

Answers on page 32.

Diabetes Medication and the Older Adult

Each year over 20,000 hospital visits are related to adverse drug events from diabetic medication use in older adults.[9] The majority of these hospital visits are due to **hypoglycemia** (blood sugars below 70 mg/dL) with older adults experiencing loss of consciousness, changes in mental functioning such as confusion and delirium, and even seizures.[9] Insulin and oral diabetic medications that cause hypoglycemia—glyburide (Diabeta, Glynase), glipizide (Glucotrol), glimepiride (Amaryl), repaglinide (Prandin), nateglinide (Starlix)—contribute to the majority of these hospitalizations.[9] Older adults are at risk for hypoglycemia for several reasons including: use of insulin or oral hypoglycemic agents or both; long duration of diabetes; decreased or erratic food consumption; reduced kidney function; slowed intestinal absorption; polypharmacy; and visual, functional, or mental impairments that may lead to medication errors.[75,76] Older adults are also at an increased risk for complications from hypoglycemia such as falls or other injury due to a decreased awareness of symptoms as a result of dementia, cognitive or mental impairment, or use of medications that mask symptoms of hypoglycemia (i.e. beta blockers—metoprolol [Lopressor, Toprol XL], carvedilol [Coreg], atenolol [Tenormin]). Severe hypoglycemia (hypoglycemia requiring medical assistance) in older adults has been associated with an increased risk for dementia as well as death.[77,78] Therefore, it is very important to teach patients and caregivers how to recognize symptoms of hypoglycemia and how to manage them appropriately.[79] Symptoms of hypoglycemia may include sweating, shakiness, nervousness, rapid heartbeat (if not taking a beta blocker), confusion, irritability, lightheadedness or dizziness, weakness, hunger, nausea, or blurred vision.[80] If the patient is conscious, ingesting 15 to 20 grams of glucose or simple carbohydrates is the preferred method for treating hypoglycemia.[79] This amount of glucose or carbohydrate is equivalent to three or four glucose tablets (refer to instructions on package), 4 ounces (1/2 cup) of orange juice or regular soda, three to five hard candies chewed quickly (refer to nutritional information on candies), one tube of glucose gel (Glutose 15), or one tablespoon of sugar, honey, or corn syrup.[80] Fifteen minutes after consuming 15-20 grams of glucose, the blood sugar should be rechecked. If hypoglycemia (blood sugar less than 70 mg/dL) persists, the patient should repeat treatment. Once the blood sugar returns to normal, instruct patients to eat a small snack if their mealtime is more than one to two hours away to prevent the hypoglycemia from reoccurring.[79,80] An intramuscular or intravenous injection of glucagon can be given if the hypoglycemic patient is not conscious.[79]

In order to prevent hypoglycemic events in older adults, blood sugar goals are often adjusted to be more lenient, especially in older adults with limited life expectancies, dementia, or advanced diabetes complications.[76] These patients are at greater risk of hypoglycemia and are also less likely to benefit from stringent blood sugar control.[75,76] In these patients, blood sugar goals should be adjusted to prevent hypoglycemia while at the same time minimizing complications from high blood sugars (greater than 180-200 mg/dL) such as dehydration, hyperglycemic crises, poor wound healing, increased urination, electrolyte changes, and falls.[75,76]

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and the Older Adult

NSAIDS such as ibuprofen (Advil, Motrin) and naproxen (Aleve, Naprosyn) are often used by older adults for the management of arthritis pain, chronic lower back pain, and gout. In fact, NSAIDs are commonly prescribed in the US with nearly 100 million prescriptions filled in 2012.[81] OTC NSAID products are also commonly purchased in the US with about 23 million Americans taking OTC NSAIDs in 2012.[81] It is estimated that more than 20% of patients over the age of 65 years are using prescription NSAIDS, and many more are using OTC NSAIDs. Although effective agents for painful inflammatory conditions, NSAIDs are not without risks, especially in vulnerable, older adult populations. In an older veteran population, NSAID use was found to be associated with an increased risk of hospitalization for GI bleeding, stomach ulcers, heart attacks, kidney failure, and heart failure.[82]

NSAIDs are typically classified by the degree to which they block or inhibit the cyclooxygenase (COX) enzymes 1 and 2. By blocking the COX-2 enzyme, NSAIDs prevent the production of certain compounds (called prostaglandins) involved in pain and inflammation. By blocking the COX-1 enzyme, NSAIDs reduce the production of "housekeeping" prostaglandins, or the substances responsible for protecting the lining of the stomach and maintaining the clotting function of platelets.[83] Most commercially available NSAIDs are classified as "nonselective" and therefore block both COX-1 and COX-2 enzymes. By blocking both of these enzymes, nonselective NSAIDs contribute to pain relief but also cause GI complications and increase the risk of bleeding by interrupting the function of the "housekeeping" prostaglandins. Many older adults are at risk for bleeding complications from nonselective NSAIDs due to age alone and due to the increased use of other medications that increase risk of

bleeding such as blood thinners, aspirin, agents like clopidogrel (Plavix), and use of steroids such as prednisone (Deltasone) or dexamethasone (Decadron).[84] Use of an NSAID and a blood thinner together may increase the risk of a GI bleed by three to six times.[85] GI bleeding and ulcers commonly occur without any warning—patients may not experience heartburn or stomach upset beforehand.[85] Due to the risk of bleeding in older adults using NSAIDs, especially those over age 75 years, nonselective NSAIDs are listed on the Beers criteria as agents to avoid.[19] If the patient cannot tolerate other pain medications and use of a nonselective NSAID cannot be avoided, the older adult should be placed on a medication to protect the stomach's lining such as a proton pump inhibitor (examples are discussed previously).[19,84] These patients should also be instructed to take NSAIDs with food to minimize contact time with the stomach's mucosal lining.[85]

COX-2 selective NSAIDs were developed to block only the COX-2 enzyme and thereby reduce the risk of GI bleeding and ulceration. Evidence suggests that COX-2 selective NSAIDs such as celecoxib (Celebrex) cause fewer serious GI complications; however, the evidence is generally limited to the first six months of use.[85] In addition, the GI protective effect of a COX-2 inhibitor may be lost if the patient is also taking a daily aspirin. COX-2 selective NSAIDs are not free of adverse effects, and compared to nonselective NSAIDS, are associated with greater risk of serious cardiovascular events such as heart attacks. Both nonselective and selective NSAIDS, however, can worsen cardiovascular diseases such as high blood pressure and heart failure by causing fluid buildup in the body. For this reason, the Beers criteria warns against the use of both nonselective and selective NSAIDs in patients with cardiovascular disease, especially heart failure.[19] Patients with a recent heart attack or open heart surgery are also at increased risk of poor outcomes with the use of NSAIDs.[85] Heart conditions such as high blood pressure, heart failure, and heart attacks are common in the older adult population. Therefore, healthcare providers must continue to educate these patients on avoiding NSAID use. All NSAIDs also have the potential to worsen kidney function, and elderly patients may be particularly sensitive to this adverse effect due to age-related kidney impairment, dehydration, and use of diuretic medications.[85] NSAID use in an older adult with cardiovascular disease or NSAID use in patients with kidney impairment are two examples of drug-disease interactions. A drug-disease interaction implies that the medication in question has the potential to worsen an underlying disease process. Therefore, healthcare professionals should be aware of not only drug-drug interactions, but also drug-disease interactions in order to prevent adverse drug events in older adults.

Test Your Knowledge #7

Mr. Baker (see Case Study 2 on page 20) has high blood pressure, heart disease, and kidney impairment. Which one of Mr. Baker's medications could worsen all three of these conditions, and therefore should be avoided?

_____

Answer on page 32.

Strategies for Improving Medication Safety in the Older Adult

As described in previous sections, older adults are at risk for adverse drug events for many reasons—multiple chronic conditions, multiple prescribers, polypharmacy, drug-drug interactions, drug-disease interactions, and changes in drug processing and sensitivity. The first step to preventing adverse drug events in older adults is to identify those patients at increased risk for adverse drug events. All older adults should be screened for the risk factors listed in **Table 1** ***(page 3)***. Patients with one or more of these risk factors should have interventions to reduce the potential for drug-related harm.[86] Interventions may include reducing polypharmacy by discontinuing potentially unnecessary medication, switching to safer alternative medications, reducing the dose of medications, monitoring drug levels, checking for signs of toxicity, or counseling the patient on adherence strategies.[87]

Medication review by a pharmacist or other qualified healthcare provider is also an important strategy to reduce medication-related problems in older adults. There are many definitions of medication review, but generally it is a process of ensuring that each medication is assessed to determine whether it is appropriate, effective, safe, and meets the patient's individual goals.[88] Before an effective medication review can be performed, an accurate medication list must be obtained from the patient. Pharmacy technicians in many different settings--community, hospital, and emergency departments--are now collecting detailed medication histories and lists from patients. To further facilitate this process, technicians may also ask older adults or their caregivers to bring in all of their medications from home. This includes prescription medications, OTC products, herbals, supplements, vitamins, non-oral medications (such as inhalers, creams, eye/ear drops, suppositories), and as needed

medications. The pharmacist should provide counseling by reviewing each of these medications with the patient to ensure the patient is taking the medication as prescribed and understands what it is for. This is also an opportunity to assess for any barriers to medication use such as cost, difficulty reading or seeing the label, and difficulty opening the medication container. Each medication should also be reviewed for potential side effects such as orthostasis upon standing as discussed earlier.[89] It is important to screen for any new symptom (such as headache, nausea, itching, drowsiness, and dizziness) as it could be attributable to an adverse drug event, side effect, or allergy to medication.[90] In older adults, in particular, it is important to identify who is the medication manager at home as many older adults may rely on the help of others for managing their medications. This person should be interviewed as well to determine how well the patient is adhering to and tolerating his or her medications.

After an accurate medication list is compiled from the patient and the caregiver, the pharmacist can assess the medication list for medication-related problems.[89,91] The different types of medication-related problems and their causes are listed in **Table 6**. A practical way to identify medication-related problems during a medication review is to match

Table 6. Pharmacists Should Screen for Medication-Related Problems in Older Adults[88,90]

Medication-Related Problem	Common Causes
Unnecessary medication therapy	• No medical condition for the medication • Duplicate therapy • Medication being used to treat a side effect of another medication • Medication not consistent with patient's individual goals
Untreated or undertreated condition	• A medical condition is not being treated • Additional medication is needed for optimal treatment of a condition
Ineffective medication	• Medical condition is not responding to the medication product • Dosage form is inappropriate • Medication product is ineffective for medical condition
Dose too low	• Dose too low or dosing frequency inadequate for desired response • Drug interaction reduces active medication available • Duration of therapy is inadequate for desired response
Dose too high	• Dose too high or dosing interval too frequent • Duration of therapy exceeds that necessary • Drug interaction increases active medication available • Rate of administration is too rapid
Adverse drug event	• Medication causes an undesirable response/reaction • Safer medication is required due to patient risk factors • Drug interaction causes an undesirable response • Dose increased/decreased or administered too rapidly • Inappropriate formulation used
Drug-disease interaction	• Medication for one medical condition worsens another medical condition (i.e. NSAID for arthritis pain may worsen heart failure, hypertension, or peptic ulcer disease)
Nonadherence	• Patient misunderstands instructions/complex medication regimen • Patient is unaware of purpose of medication • Patient does not want to take the medication (experiencing side effects or perceives medication as ineffective or unnecessary) • Patient forgets to take medication (memory difficulties) • Patient is unable to swallow or self-administer medication (i.e. inhaler, eye drops, injection) • Packaging difficulties (cannot open package or read label) • Medication is expensive/drug availability issues

each of the patient's medications with his or her medical conditions. This will help highlight medications that are being prescribed for or purchased by the patient without a legitimate medical need. It will also help identify gaps in treatment such as medications that should be prescribed but were not. Each medication should also be scrutinized for its potential harm to the older patient. Healthcare providers can refer to the Beers criteria to identify potentially inappropriate medications in older adults.[19] As mentioned previously, several medication classes are listed on the Beers criteria and should be avoided in older adults such as anticholinergic medications **(Figure 2, *page 16*)**, benzodiazepines, sleep aids, the new blood thinners in patients with poor kidney function, and nonselective NSAIDs.[19] The STOPP criteria provides a list of potentially inappropriate medications for common conditions in older adults and is another screening tool that may be utilized during a medication review.[20,21] Sometimes medications are under-prescribed in the older adult population such as blood thinners for stroke prevention as discussed previously. Therefore, the START criteria, which stands for **S**creening **T**ool to **A**lert to the **R**ight **T**reatment, can also be used to help prescribers identify important medications that may be missing, such as cholesterol medications in older adults under age 85 years with a history of stroke or heart attack.[20,21] Yet another tool that can be used to assess medication appropriateness in the older adult is the medication appropriateness index (MAI). This tool consists of ten questions to think about when assessing each medication for an individual patient **(Table 7)**. The MAI evaluates ten core domains of medication appropriateness: medical indication, medication effectiveness, dose, correct medication directions, practical directions, drug-drug interactions, drug-disease interactions, duplicate medication therapies, length (i.e. number of days, weeks, etc) of treatment, and cost.[86,92]

Table 7. Medication Appropriateness Index (MAI)[91]

Questions to ask about each individual medication:
1. Is there a medical indication for the medication?
2. Is the medication effective for the medical condition?
3. Is the dose correct?
4. Are the directions correct?
5. Are the directions practical for the patient?
6. Are there any drug-drug interactions with this medication?
7. Are there any drug-disease interactions with this medication?
8. Is there unnecessary duplication with other medications?
9. Is the length of treatment acceptable?
10. Is this medication the least expensive or are there more cost-effective alternatives?
Modified from reference 91

After all medication-related problems have been identified, a plan should be developed to resolve these problems.[87] Oftentimes, this requires collaboration among all members of the patient's healthcare team—pharmacists, physicians, nurses and nurse practitioners, physical therapists, social workers, and other healthcare providers including pharmacy technicians. At the center of the healthcare team is the patient and his or her caregivers; therefore, it is important to involve the patient and caregivers in medication decisions to ensure adherence and understanding of any medication-related changes. A significant component of the plan should revolve around removing barriers to nonadherence as well as targeted patient education.[89] One of the most important interventions for improving adherence involves simplifying medication regimens. Studies have shown that medication adherence decreases significantly for patients taking medications multiple times per day instead of just once daily.[93] Other adherence strategies include improving organizational skills by using pill organizers (i.e. pillbox), medication calendars, and involving family members. If patients have difficulty using certain devices or medication products or have difficulty swallowing large tablets, modifications to therapies should be made. Cost is often a large barrier for patients, and therefore selecting lower cost medications and assessing prescription drug insurance can be effective strategies for improving adherence. Pharmacy technicians may be particularly skilled in this area and can be important team members to involve in developing medication-related plans.

If changes have been made to the patient's medication list, electronic medical records should be updated to reflect the most current medication list. This is such an important strategy for preventing medication errors and preventing adverse drug events that it is considered a quality indicator for medication use in vulnerable adults.[94] An accurate, updated medication list should also be provided to the patient and caregiver with a summary of key details: medication name, purpose, dose, and dosing schedule. The list should be written in patient-friendly language, and the patient should be instructed to share this list with other healthcare providers as well as keep a copy for themselves (i.e. in wallet). Simply providing a list of updated medications to the patient may not be enough

to improve adherence and ensure safe medication use. In depth, one-on-one medication education should also be provided with thorough explanation of the rationale for each medication.[94] Pharmacists and prescribers should provide the following information when discussing each medication with patients and caregivers:[95]

- Drug name (both brand and generic)
- Medical indication for each medication
- Rationale or anticipated benefit of the medication such as impact on disease progression, hospitalization, survival, and quality of life
- Appropriate use: dose, dosing schedule (which includes discussion of timing as it relates to food and other medications), storage, and how to manage missed doses
- Duration (length) of use
- Side effects (especially when starting or increasing a medication)

Lastly, an important step in ensuring medication safety in older adults is regular follow-up with patients and review of medication regimens. At a minimum, older adults should have an annual medication review by qualified healthcare professionals.[94] Changes in mental status, function, new or increasing falls, and recent hospitalization should also trigger a medication review due to possible new medication-related problems.[89] As evident in this section, preventing adverse drug events and ensuring medication safety in the older adult is a dynamic process that requires understanding of age-related changes, recognition of potential inappropriate or high risk medications, and thorough patient screening, education, and frequent follow-up.

Conclusion

Caring for older adults with multiple chronic conditions and complex medication regimens can be challenging, and this challenge is only going to increase with the projected growth of the older adult population. In order to ensure medication safety in an older, vulnerable population, healthcare professionals must understand age-related changes in drug processing and drug sensitivity, identify patients with additional risk factors for adverse drug events, and recognize potentially inappropriate medication therapies. With new medications reaching the market every day, it is also critical that clinicians caring for older adults stay up-to-date with not only the benefits of new medication therapies but with the potential risks (harm) as well. Pharmacy technicians, as members of the healthcare team, should continue to increase their knowledge of appropriate medication use in older adults to support the pharmacist in identifying patients needing medication review, education, and interventions.

APPENDIX A

Glossary of Terms:

Absorption: process by which a medication reaches the bloodstream after it is administered to the patient.[24]

Acetylcholine: the neurotransmitter in the brain responsible for memory, thinking, and language.

Adverse Drug Event: injury, harm, or undesirable health outcome due to drug therapy.[5]

Anticholinergic medications: medications that block the activity of acetylcholine at cholinergic neurons.

Cardiovascular System: a system composed of the heart and blood vessels that functions to move blood through the body.

Central Nervous System: a system composed of nerve tissues (brain, spinal cord) and controls activities of the body.

Creatinine Clearance (CrCl): an estimate of how well the kidneys are filtering and excreting drugs.

Distribution: the movement of a drug from the bloodstream to the body's tissues.[24]

Elimination: a final pharmacokinetic process that involves "removal of drugs from the body."[24]

Enteric-coated: a special coating that prevents a drug from being dissolved in the stomach, thereby allowing the drug to dissolve in the small intestine.

Extended-release medications: a medication formulation that allows a drug to be released slowly over time.

Fall: an event that causes a patient to unexpectedly come to rest on the floor, ground, or other lower level.[12,13]

Fat-soluble: drugs that readily dissolve in fat.

First-pass effect: A phenomenon that occurs when orally administered medications move through the wall of the intestine and pass through the liver where some of the medication is chemically broken down before entering the bloodstream. Sometimes this effect is called "first-pass metabolism" because of the actions occurring in the liver. Medications delivered by other routes (intravenous, intramuscular, subcutaneous, and sublingual) are not subject to this first-pass effect.

Frailty: is a progressive decline associated with advanced age and characterized by weight loss, loss of strength and balance, fatigue, impaired memory and function, and dependence on others for care.[16,17]

Hypoglycemia: blood sugars less than 70 mg/dL.

Medication review: a structured assessment of medication regimens by a pharmacist or other qualified healthcare professional such as a physician or advanced practice nurse. The goal of this activity is "to evaluate and optimize medi-cation by providing a recommendation or by making a direct change."[22]

Metabolism: the "chemical alteration of a drug by the body," primarily taking place in the liver.[24]

Metabolite: a product of metabolism that is different from the original drug.

Pharmacodynamic: the effect of a drug on the body. Simply put, it is "what the drug does to the body."

Pharmacokinetic: the processes by which a drug moves through the body (absorption, distribution, metabolism, elimination). Simply put, it is "what the body does to a drug."

Phase I metabolism: metabolism that relies on enzymes produced in liver cells (called cytochrome P-450 or CYP enzymes).

Phase II metabolism: metabolism in the liver by means other than cytochrome P-450 enzymes.

Polypharmacy: the use of multiple medications (typically four or more) including complex medication regimens and potentially unnecessary medications.[10]

Psychotropic: a term to describe medications that can affect the mind, mood, or behavior.

Orthostatic hypotension: a reduction in systolic blood pressure of 20 mmHg or more or a reduction in diastolic blood pressure of at least 10 mmHg within 3 minutes of standing.[43]

Water-soluble: drugs that readily dissolve in water.

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EDITOR'S COMMENTS: A summary of the Beers criteria can be found at https://www.guideline.gov/summaries/summary/49933/american-geriatrics-society-2015-updated-beers-criteria-for-potentially-inappropriate-medication-use-in-older-adults?q=Beer

ANSWER KEY: TEST YOUR KNOWLEDGE EXERCISES

Exercise #1:

1. Age ≥ 85
2. Five or more medications
3. Multiple chronic conditions
4. Multiple prescribers (Dr. Potter and the heart specialist)
5. Depression
6. Recent hospital visit
7. Poor kidney function
8. History of adverse drug event (history of falls may be due to inappropriate medication use)

Refer to Table 1 (page 3) for a list of risk factors associated with adverse drug events.

Exercise #2:

1. True
2. False

Explanation: In older adults, body fat can increase by 25% to 30%. This higher percentage of body fat may cause fat-soluble medications to accumulate in tissues, increasing the risk for toxicity. In contrast, total body water decreases with age. In older adults, water-soluble medications may achieve higher blood levels, which increases the risk for toxicity.

Refer to Table 3 (page 10) for a summary of age-related changes in older adults.

Exercise #3:

1. A
2. A
3. B
4. B
5. A

Explanation: Psychotropic medications such as the benzodiazepine, lorazepam (Ativan), for anxiety, and the tricyclic antidepressant, amitriptyline (Elavil), may contribute to falls in the older adult due to effects on the central nervous system such as sedation and balance issues. Mrs. Smith's medications for blood pressure such as amlodipine (Norvasc) and metoprolol (Lopressor, Toprol XL) may also cause dizziness and lightheadedness upon standing and contribute to falls as discussed in the section "Aging and the Cardiovascular System." Oxybutynin (Ditropan) is an anticholinergic medication as discussed in the section "Aging and the Central Nervous System" and may cause balance difficulties and negatively affect physical function.[10] However, evidence describing a direct link between anticholinergic use and falls is limited.[10]

Exercise #4:

_____ aspirin
_____ meclizine
_X__ terazosin
_X__ furosemide
_X__ quetiapine

Explanation: Medications affecting the cardiovascular system such as terazosin (Hytrin) and furosemide (Lasix) can cause orthostatic hypotension. Many non-cardiovascular medications can also cause orthostatic hypotension such as the anti-psychotic quetiapine (Seroquel).

Exercise #5:

_____ terazosin
_X__ meclizine
_____ ibuprofen
_X__ paroxetine
_____ omeprazole

Explanation: Meclizine (Antivert) and paroxetine (Paxil) are anticholinergic medications that may cause memory and thinking impairments, drowsiness, constipation, dry mouth, increased heart rate, dry eyes, blurred vision, and urinary retention. Other medications with strong anticholinergic potential are shown in Figure 2 (page 16).

Exercise #6:

1. D
2. E
3. B
4. C
5. A

Explanation: Five oral blood thinners are available for the treatment and prevention of strokes and blood clots. Selection of the most appropriate blood thinner requires careful consideration of kidney and liver function, drug cost, drug interactions, adherence (taking the medication as prescribed), history of GI bleeding, cognitive ability, and patient preference.

Exercise #7:

Ibuprofen

Explanation: Nonselective NSAIDs such as ibuprofen (Motrin, Advil) and selective NSAIDs such as celecoxib (Celebrex) can worsen blood pressure, heart disease particularly heart failure, and impair kidney function. Refer to the section "Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and the Older Adult."

SELF ASSESSMENT QUESTIONS

1. **By 2060, how many people in the United States will be over 65 years of age?**
   A. 9,800
   B. 98,000
   C. 980,000
   D. 98,000,000

2. **The use of multiple medications including complex medication regimens and potentially unnecessary medications is known as:**
   A. Pharmacotherapy
   B. Polypharmacy
   C. Therapeutic Duplication
   D. Adverse Drug Event

3. **Which of the following increases an older adult's risk for adverse drug events?**
   A. Living at home
   B. Recent visit to a physician's office
   C. Multiple chronic conditions
   D. Use of one pharmacy

4. **Which of the following are frequently associated with emergency hospitalizations among older adults?**
   A. Warfarin (Coumadin)
   B. Atorvastatin (Lipitor)
   C. Insulin
   D. Both A and C

5. **Medications associated with falls in the older adult typically affect which two body systems?**
   A. Central Nervous System and Cardiovascular System
   B. Digestive System and Skeletal Muscle System
   C. Endocrine System and Cardiovascular System
   D. Central Nervous System and Genitourinary System

6. **Drug processing, or pharmacokinetics, consists of these four key stages:**
   A. Absorption, Modification, Catabolism, and Excretion
   B. Absorption, Distribution, Catabolism, and Elimination
   C. Absorption, Distribution, Metabolism, and Elimination
   D. Administration, Modification, Metabolism, and Elimination

7. **If an older adult is having difficulties swallowing, certain medications may be crushed and placed in soft food. Which of the following should NOT be crushed?**
   A. Enteric-Coated Tablets
   B. Oral Disintegrating Tablets
   C. Extended Release Products
   D. Both A and C

8. **Which of the following is true of age-related changes in body composition?**
   A. Body fat increases with age
   B. Body fat decreases with age
   C. Body water increases with age
   D. There are no changes in body fat or body water with age

9. **Because kidney function decreases with age, which of the following is true?**
   A. Fat-soluble medication will accumulate
   B. Phase II metabolism will decrease
   C. Medication doses should be increased
   D. Medication dose reductions may be needed

10. **Older adults are often prone to decreases in systolic blood pressure upon standing. What is this phenomenon called?**
    A. Hypertension
    B. Vertigo
    C. Orthostatic Hypotension
    D. Hypoglycemia

11. Anticholinergic medications can cause which of the following adverse effects?
A. Diarrhea
B. Drowsiness
C. Stomach ulcer
D. Swelling

12. Which of the following is a medication with strong anticholinergic properties and should be avoided in older adults?
A. Omeprazole (Prilosec)
B. Ibuprofen (Advil, Motrin)
C. Diphenhydramine (Benadryl)
D. Metoprolol (Lopressor, Toprol XL)

13. Benzodiazepines should be avoided in older adults. All of the following are benzodiazepines, except for which one?
A. Alprazolam (Xanax)
B. Mirtazapine (Remeron)
C. Clonazepam (Klonopin)
D. Diazepam (Valium)

14. All of the following are blood thinners, except for which one?
A. Apixaban (Eliquis)
B. Rivaroxaban (Xarelto)
C. Dabigatran (Pradaxa)
D. Amitriptyline (Elavil)

Questions 15-18 refer to the following case:

Mrs. Smith is a 91-year-old female patient with many chronic conditions including diabetes, high blood pressure, heart failure, high cholesterol, and arthritis. She was recently diagnosed with a blood clot in her left lower leg and was started on the blood thinner warfarin (Coumadin) to treat it. She is also taking aspirin daily for heart health, naproxen (Aleve) twice daily for her arthritis pain, glyburide (Diabeta) for diabetes, atorvastatin (Lipitor) for her cholesterol, and metoprolol (Lopressor) for her heart failure and high blood pressure. Mrs. Smith tries to eat very healthy. She eats calcium-containing foods and has multiple servings of vegetables, such as broccoli and brussel sprouts every day. She also watches her sodium intake, but does drink 2-3 cups of coffee daily.

15. What in Mrs. Smith's diet most likely interacts with warfarin?
A. Calcium
B. Broccoli
C. Low Sodium
D. Coffee

16. What risk factor does Mrs. Smith have that may increase her risk of bleeding while taking warfarin?
A. High cholesterol
B. Aspirin use
C. Caffeine consumption
D. Use of multiple pharmacies

17. Which medication increases Mrs. Smith's risk for hypoglycemia (low blood sugar)?
A. Warfarin
B. Naproxen
C. Atorvastatin
D. Glyburide

18. Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) that may worsen which of Mrs. Smith's chronic conditions?

A. High blood pressure and heart failure
B. Diabetes and high cholesterol
C. High cholesterol and arthritis
D. Arthritis and diabetes

19. All of the following are strategies to improve medication safety in older adults, except for which one?

A. Providing thorough medication education to patients
B. Performing a comprehensive medication review
C. Utilizing tools such as the STOPP/START criteria
D. Admitting older adults to long term care facilities

20. To avoid medication errors and to increase adherence, patients should be provided with updated, accurate medication lists containing what information?

A. Medication name, dose, and quantity
B. Medication name, purpose, dose, and dosing schedule
C. Medication name, dose, and dosing schedule
D. Medication name, dose, and number of refills