Understanding the Pharmacology of Aging

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Cover Illustration by Christie Grams
Understanding the Pharmacology of Aging

INTRODUCTION

Adults age 65 years and older currently comprise approximately 13% of the US population but consume 30% of all prescription drugs and 40% of all nonprescription drugs. In the last decade, the geriatric age group accounted for one third of the overall health expenditure in the United States; by 2004, the health care cost for this group is projected to be 50% of the national health care bill. A substantial portion of this amount will be spent on medications.

Medication use steadily increases with age in older adults because of increasing comorbidity. On average, an older adult uses 3 or more medications at any given time; 2 of every 5 drugs taken are bought over-the-counter. Residents of long-term care facilities take an average of 5 to 8 prescriptions, not including medications taken on an as-needed basis. Polypharmacy (the administration of several drugs concurrently) is associated with an increase in the incidence of adverse drug events (ADEs); adverse reactions are implicated in 10% to 17% of hospital admissions of older patients in the United States. In nursing homes, for each dollar spent on medication, $1.33 is spent in the treatment of drug-related consequences. Hence, it is imperative for physicians to understand the age-related changes in pharmacokinetics and pharmacodynamics in order to prescribe appropriately in this age group.

The Nursing Home Reform Amendments of the Omnibus Budget Reconciliation Act of 1987 mandated that the Health Care Financing Administration establish regulations that include the use of medications in nursing homes. Explicit criteria that have been published regarding medication use relate to dosing and frequency, and include information on medications to be avoided in ambulatory geriatric patients.

AGE-RELATED CHANGES IN PHARMACOKINETICS

Pharmacokinetics is the study of the absorption, distribution, metabolism, and excretion of drugs. Pharmacodynamics is the study of the biochemical and physiological effects of drugs. Simply stated, pharmacokinetics is “what the body does to the drug,” whereas pharmacodynamics is “what the drug does to the body.” Figure 1 provides a schematic representation of the drug pathway. Age-related physiologic changes that affect pharmacokinetics are summarized in Table 1.

ABSORPTION

Absorption refers to the movement of a drug from the site of administration to the intravascular space. Bioavailability is the fraction of an administered drug that reaches the circulation. The bioavailability of an intravascular medication is 100%, whereas that of an oral drug is lower, depending on the amount absorbed from the gastrointestinal tract during first-pass metabolism (ie, extraction by the liver, or pre-systemic clearance).

Age-related changes in the gastrointestinal system include decreased splanchnic perfusion and mucosal atrophy of the intestines. Changes in acid secretion are minimal to nonexistent. These age-related changes may theoretically lessen drug absorption. In reality, however, the absorption of most oral drugs—although marginally slower—is, in fact, complete. Absorption of drugs occurs generally through passive diffusion, a process that is not altered with aging.

DISTRIBUTION

The volume of distribution of a drug is determined by comparing the amount of drug in the body to the concentration measured in the plasma or serum. It depends on the plasma protein–binding and tissue-binding properties of the drug, as well as its lipid-to-water coefficient. The volume of distribution is useful in determining the loading dose of a drug:

\[
\text{Volume of distribution} = \frac{\text{amount of drug in body}}{\text{concentration}}
\]

\[
\text{Loading dose} = (\text{desired concentration}) \times (\text{volume of distribution})
\]

There are 2 major plasma proteins with drug-binding qualities: albumin and α1-acid glycoprotein (AAG). Levels of AAG are not affected by age. Levels of albumin are not affected by age per se, but they may decline in association with disease. Albumin binds acidic drugs (eg, warfarin, phenytoin) whereas AAG preferably binds basic drugs (eg, lidocaine, propranolol). The albumin level should be considered when interpreting plasma drug concentration, which measures total drug levels (ie, protein-bound [inactive] as
well as free [active] drug). When the albumin level is low, the fraction of free (active) drug is greater. Hence, at therapeutic concentrations, a drug may exert a greater effect when its free component is high as a result of lower levels of plasma-binding proteins. Warfarin, which is 99% protein-bound, has increasing anticoagulant activity and toxicity in patients with decreased albumin levels.8

Aging is associated with an increase in total body fat, with a concomitant decrease in total body water and lean body muscle mass. When administering water-soluble drugs to older patients, lower doses are required to achieve the desired drug concentration; using standard doses recommended for younger adults may result in supernormal drug concentrations. Hence, water-soluble drugs such as lithium, digoxin, and aminoglycosides need lower maintenance doses to avoid ADEs.1 On the other hand, lipid-soluble drugs, (eg, benzodiazepines), have an increased volume of distribution in older patients. With these drugs, sufficient time should be allotted for the drug to reach steady-state concentration before increasing the dose or changing the drug because of an apparent lack of efficacy. Lipid-soluble drugs remain in the fat depots for prolonged periods of time.

Figure 1. Schematic representation of drug pathway.
exerting their effect long after the drug has been withdrawn. Hence, vigilance for toxic effects is needed even after discontinuing the drug.

**METABOLISM AND CLEARANCE**

A drug is eliminated from the body primarily via the liver and/or the kidneys. Total drug clearance (Cl total) is the sum of all the drug clearances from the body, measured in unit of volume of drug cleared per unit time. The higher the clearance rate of a drug, the more frequent its dosing rate.

\[
\text{Cl total} = \text{Cl hepatic} + \text{Cl renal} + \text{Cl other}
\]

Sites of metabolism and excretion of several commonly used drugs are shown in **Table 2**.

**Drug Metabolism and Clearance in the Liver**

Drugs are metabolized in the liver by phase I or phase II metabolism. Phase I metabolism, which comprises oxidation, reduction, and hydrolysis, declines in the elderly as a result of a decrease in hepatic blood flow parallel to a decline in cardiac output—the blood flow to the liver decreases to nearly half by age 85 years.10 Examples of drugs affected by reduced phase I metabolism include diazepam and flurazepam with resultant prolonged duration of activity of the parent drug and/or its active metabolite. Phase II metabolism—primarily conjugation (ie, glucuronidation, sulfation, and acetylation)—is less affected by aging. Examples of drugs affected by phase II metabolism include lorazepam, oxazepam, and temazepam;11 the activity and half-life of these drugs do not change significantly with aging. Although no satisfactory algorithms exist for calculating the dose of hepatically metabolized drugs, in practice, their dose may be reduced in the elderly.

The cytochrome P-450 (CYP) system is the supergene family of enzymes involved in oxidative metabolism. The system comprises 3 major groups: CYP1, CYP2, and CYP3A; the last group accounts for the metabolism of approximately 50% of drugs.8 Drug
metabolism by CYP may be minimally altered in the elderly due to the effect of age alone. However, many drugs and other substances alter the effects of CYP enzymes (Table 3), and thus the use of multiple drugs for comorbid processes may result in significant changes. In older individuals who take multiple drugs, therefore, it is important to be aware of common hepatic enzyme inducers and inhibitors with a potential for drug-drug and drug-food interactions. Induction and inhibition of enzymes result in faster or slower clearance of drugs, respectively. Rifampin is best known for its CYP-inducing capabilities; administration of rifampin results in a many-fold increase in hepatic clearance of other administered drugs, including dihydropyridine calcium channel blockers, phenytoin, and statins. Recognized CYP inhibitors include cimetidine, erythromycin, quinolones, and grapefruit juice.8

Drug Clearance in the Kidneys

Drugs reaching the kidneys for clearance via renal blood flow undergo glomerular filtration (unbound drugs), tubular secretion (protein-bound drugs), or tubular reabsorption.8 Glomerular filtration rate (GFR) is approximated by calculating the creatinine clearance. With aging, creatinine clearance declines by approximately 1 mL/min annually (10 mL/min per decade).9 This change, which is attributed to a decrease in renal blood flow and reduction in renal mass, is not invariable. Further, alterations in renal function may frequently occur from disease. Creatinine clearance utilizing the formula by Cockroft and Gault12 should be calculated in all older adults prior to drug administration:

\[
\text{Creatinine clearance (in males) } = \frac{(140 - \text{age in years}) \times (\text{body weight in kg})}{72 \times \text{serum creatinine concentration in mg/dL}}
\]

In females, the result is multiplied by 0.85.

The serum creatinine value by itself may not accurately reflect the renal status in the elderly because of sarcopenia, or loss of muscle mass with age. A specific serum creatinine value in younger versus older adults may represent differing creatinine clearances; an older adult with a given serum creatinine value will likely have a lower GFR. Although a 24-hour urine collection can be used to determine the creatinine clearance, its use in the elderly is cumbersome and often is not practical.

Drug Clearance in Other Sites

Although most drugs undergo clearance via the kidney or liver, other sites contain metabolic enzymes similar to those found in the liver. Some CYP enzymes have been located in the gastrointestinal tract mucosa, kidneys, lungs, brain, skin, leukocytes, and bone marrow. When intestinal CYP3A4 is inhibited by grapefruit juice, the action of certain oral drugs such as nifedipine, terfenadine, and triazolam is prolonged.8

Drug Half-life

A drug’s half-life refers to the time taken for the drug concentration to decrease by 50% after drug distribution in the body; it is affected by the changes in drug distribution and clearance already described. With aging, an increase in elimination half-life has been observed with several drugs.8

Table 3. Common Inhibitors and Inducers of Cytochrome P-450 Enzymes

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Charbroiled meat</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Morphine</td>
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<tr>
<td>Erythromycin</td>
<td>Omeprazole</td>
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<tr>
<td>Fluconazole</td>
<td>Phenobarbital</td>
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<tr>
<td>Fluoxetine</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Prednisone</td>
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<tr>
<td>Haloperidol</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Tobacco smoking</td>
</tr>
<tr>
<td>Sertraline</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
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</tr>
</tbody>
</table>

AGE-RELATED CHANGES IN PHARMACODYNAMICS

At a given site of drug action, the response elicited may be qualitatively or quantitatively different in older adults as compared with younger adults. These differences may result from several factors.

HOMEOSTASIS

Homeostatic mechanisms provide the means by which the body can adjust or counteract a particular drug effect. For example, in a young adult taking morphine, the expected depression of the respiratory center is counteracted by reflex stimulation of the respiratory system. In older patients taking morphine, however, blunted homeostatic mechanisms predispose to respiratory depression; sedation and constipation may also
result if the drug is given at doses meant for younger patients. Less active baroreceptor reflexes may predispose geriatric patients on antihypertensive drugs to postural hypotension, and an impaired thermoregulatory response to cooling may predispose those taking barbiturates or phenothiazine to hypothermia.13

CHANGES RELATED TO ORGAN DISEASE

Multiple comorbid conditions in an older adult may necessitate the use of a larger number of drugs, which in turn increases the risk of ADEs and drug-drug interactions. Further, organ disease itself may increase the likelihood of an adverse drug reaction. For example, a patient with glaucoma will experience elevation of intraocular pressure when on antidepressants with strong anticholinergic properties.13

RECEPTOR AND POSTRECEPTOR MECHANISMS

It is theorized that changes in the sensitivity of receptors occur with aging. Sensitivity of receptors may decrease, increase, or remain unaltered. For example, the activity of β-adrenergic receptors diminishes with age; the observed diminution in activity may be from changes in receptors or post-receptor sites.13 Therefore, a larger dose of β-agonist or antagonist agents may be required to produce a given response. On the other hand, increased sensitivity of receptors is noted with opioids and benzodiazepines, with a resultant increase in side effects. Lastly, no change in activity is noted with α-receptors; α-blockers and agonists are expected to produce the usual response in geriatric patients.

ADVERSE DRUG EVENTS

An ADE is an unintentional side effect or toxicity resulting from the administration of a drug at the recommended dose for diagnosis, prevention, or treatment. ADEs are common; they may account for 10% to 17% of hospitalizations in older adults and have been reported as one of the leading causes of death in this population.2 Still, the true incidence and reporting of ADEs are probably underestimated.

Age per se is not a risk factor for ADEs, although they do occur more frequently in the elderly. A correlation exists between increasing adverse reactions and increasing number of drugs taken.1 Most adverse drug reactions are predictable and dose-related; some, however, are idiosyncratic.1

An ADE can either be a side effect or a toxic effect from drug administration. Side effect refers to the undesirable effect of a drug that is related to its principal action (eg, orthostasis from antihypertensives). A toxic effect is an undesirable effect of a drug that is not related to its principal action (eg, hyponatremia from carbamazepine).13 Any symptom in the elderly may be considered an adverse effect until proven otherwise.

POLYPHARMACY

Polypharmacy—the administration of multiple concurrent medications—is common among the elderly. Polypharmacy may result in an ADE or drug-drug interaction. Although older patients often have multiple illnesses requiring medication, the number of medications can frequently be reduced. Physician awareness helps minimize the problem. Physicians should strive to utilize nonpharmacologic measures (eg, lifestyle modification) when appropriate, to avoid “reflex prescribing” for every identified problem experienced by a patient, and to review all drugs taken by a patient on a regular basis. Visits to multiple physicians may contribute to the problem of polypharmacy. The “paper [or plastic] bag test” is recommended, wherein all prescription and over-the-counter medications are brought in by the patient and/or caregiver for physician review at every visit.

DRUG INTERACTIONS

Drug interactions can be pharmacokinetic- or pharmacodynamic-based. Interactions occur when a drug’s action is altered by the presence of disease (drug-disease), by the intake of food (drug-food), or by another drug (drug-drug).

Drug-Disease Interactions

Drug-disease interactions occur because of the high prevalence of diseases in older adults, requiring the use of multiple drugs. Diseases may affect the organs involved in drug metabolism and excretion (mainly, liver and kidney) or the delivery of drugs to these sites. On the other hand, drugs can worsen manifestations of some diseases.1 Examples include: (1) urinary retention in the presence of benign prostatic hyperplasia or cognitive deterioration in Alzheimer’s disease resulting from the use of anticholinergic medications; (2) decline in blood pressure and/or cardiac decompensation from the use of nonsteroidal anti-inflammatory drugs (NSAIDs) through salt and water retention; and (3) bradycardia in the presence of sick sinus syndrome from the use of β-blocker topical (ophthalmic) preparations through nasal absorption and systemic effects.

Drug-Food Interactions

Drug-food interactions affect the stability or disposition of food or drug components. Such interactions may
result in a nutrient deficiency, reduced drug efficacy, or an unanticipated drug effect. Knowledge of food intake in relation to timing of drug administration, thus, becomes important. There are 4 types of drug-food interactions:\textsuperscript{14}

1. **Physicochemical or chemical interactions in vitro.** An example is the destruction of thiamine by sulfites (antioxidants used in food and drug preservation).

2. **Physicochemical interactions in the gastrointestinal tract.** Examples include decreased levodopa absorption associated with high-protein diets, osteoporosis caused by phenytoin’s effects on intestinal calcium absorption, and poor bioavailability of alendronate resulting from concomitant food intake.

3. **Metabolic interactions.** Examples include grapefruit juice potentiating the effect of nifedipine by inhibiting intestinal CYP3A4 metabolism; CYP induction by phenytoin producing ineffective vitamin D metabolites; and green leafy vegetables diminishing the effect of warfarin.

4. **Functional interactions.** An example is protein-energy malnutrition resulting from digoxin-induced anorexia.

**Drug-Drug Interactions**

Drug-drug interactions occur when 2 or more medications are used concomitantly. Interactions may involve the absorption, distribution, metabolism or elimination of medications. Examples of drug-drug interactions include cimetidine and ciprofloxacin interfering with the metabolism of theophylline, which increases its levels. NSAIDs antagonize the efficacy of several antihypertensives (eg, captopril). Salicylates, NSAIDs, and thyroxine all interact with warfarin, potentiating its anticoagulant effect.\textsuperscript{15}

**Nomenclature**

In particular, short-acting and extended-release preparations of the same drug, with differing kinetics, are used interchangeably due to failure to add the suffix to the brand name when prescribing (eg, Procardia XL [nifedipine] and Sinemet CR [carbidopa-levodopa]). Furthermore, extended-release preparations, which in general are not meant to be broken or crushed, are not infrequently administered through a feeding tube, considerably altering their properties.\textsuperscript{18}

**Illegible or Poor Handwriting**

If the prescribing physician’s handwriting is difficult to read, patients may receive a different drug or the wrong dosage. For example, levothyroxine 12.5 mcg (micrograms) is sometimes mistakenly interpreted as 12.5 mg. Orders may also be misinterpreted by hospital or pharmacy staff.

**FINANCIAL BURDEN**

The financial impact of drug prescriptions on the patient deserves consideration. The cost of many medications is prohibitive to those with inadequate prescription insurance coverage. Affordability may play a role in compliance. For outpatients, Medicare does not currently cover the cost of prescription drugs. Patients with prescription benefits are more likely to fill their prescriptions as compared with those who do not have coverage.

**PRECAUTIONS WITH SELECT DRUGS**

**Oral Hypoglycemic Agents**

The sulfonylurea chlorpropamide should be avoided in the elderly. Its long half-life predisposes to hypoglycemia, and its excretion is dependent on renal clearance. As renal function worsens, risk of hypoglycemia increases. Further, chlorpropamide can cause hypotension by stimulating antidiuretic hormone secretion.\textsuperscript{7} The sulfonylureas glyburide and glipizide are similar in efficacy and may be preferred. Glipizide absorption is reduced with food intake, whereas glyburide can be administered with or without food.\textsuperscript{2}

**Psychotropic Agents**

**Antidepressants.** The tertiary amines amitriptyline and imipramine are antidepressants generally not recommended for use in the elderly because of their potent anticholinergic and sedating effects.\textsuperscript{7} Further, orthostatic hypotension may occur because of an α-adrenergic blockade.\textsuperscript{5} Secondary amines (eg, nortriptyline, desipramine) are preferable, having the same benefits with fewer side effects.
Among the selective serotonin reuptake inhibitors, fluoxetine (with its active metabolite) has the longest half-life and hence should be used with caution; alternate-day dosing may be an option. Fluoxetine has been associated with anorexia and nausea. Sertraline and paroxetine have shorter half-lives. All three of these drugs appear to be metabolized by the CYP system.

Immediate-release bupropion is associated with dose-dependent seizure activity; the sustained-release form is preferred for elderly patients. The immediate-release form of venlafaxine (a serotonin-norepinephrine reuptake inhibitor) is associated with dose-dependent hypertension, and thus the extended-release form is recommended in the elderly. Trazodone, although useful for its sedative properties, has been associated with priapism (rarely).

In general, all antidepressants may cause hyponatremia in patients with predisposing factors for low serum sodium.

**Anxiolytics.** Benzodiazepines are used as anti-anxiety medications, anticonvulsants, muscle relaxants, and sedative/hypnotics. If possible, long-acting benzodiazepines such as diazepam, chlordiazepoxide, and flurazepam should be avoided in older patients because of tendency to have prolonged accumulation in the lipid depots. These drugs can cause daytime drowsiness, impair cognition, and increase body sway, leading to a tendency toward falling. When benzodiazepines are needed, drugs with a shorter duration of action (eg, lorazepam, oxazepam, or alprazolam) are preferred because dosing can be flexible and because these agents do not carry the cumulative toxicity risk that is associated with the longer-acting benzodiazepines. The chronic use of benzodiazepines should be avoided; their use for insomnia should be restricted to intermittent or short-term use, usually for no more than 3 weeks. Benzodiazepines should be tapered slowly when possible to avoid a withdrawal reaction.

**Antipsychotics.** Risperidone, a new neuroleptic, is an alternative to haloperidol. Its active metabolite (9-OH risperidone) is cleared by the kidneys, and thus the maintenance dose must be decreased in patients with significant renal insufficiency. Risperidone blocks α-1 receptors; this may cause orthostatic hypotension in geriatric patients. In general, antipsychotic agents are not effective when used on an “as needed” basis only.

**Antiepileptic Drugs**

As a CYP system inducer, phenytoin interacts with several medications and thus must be used cautiously in geriatric patients. Phenytoin is highly bound to albumin; no dose adjustment is necessary for age or renal status.

Carbamazepine induces its own hepatic metabolism (autoinduction); thus, after reaching its steady state concentration, half-life is reduced and plasma levels of the drug decrease. Drug levels of carbamazepine should be monitored.

**Cardiac Medications**

Because of the age-related decline in creatinine clearance, digoxin dosing must be adjusted downward in geriatric patients; accumulation of digoxin can cause anorexia, delirium, and cardiac toxicity. The benefits of digoxin in cardiac failure associated with sinus rhythm are debatable. Concomitant administration of quinidine, verapamil, or erythromycin results in increased levels of digoxin.

Blood levels of procainamide and its active metabolite (N-acetylprocainamide) increase with impaired renal function. The accumulation of procainamide can induce arrhythmias (in particular, torsades de pointes). Long-term use may cause drug-induced lupus. When administering procainamide in older patients, reduced dosages should be used and blood levels monitored.

**Anticoagulant and Antiplatelet Medications**

The use of anticoagulants in the elderly deserves special mention. The pharmacokinetics and dynamics of heparin and warfarin are altered with aging and carry an increased risk of anticoagulant-related bleeding. Older adults are 3 times more likely to bleed during heparin therapy than younger patients. Heparin use is associated with hyperkalemia and thrombocytopenia; long-term use is associated with osteoporosis.

Older adults have increased sensitivity to warfarin, although the mechanism is not clear. The same plasma warfarin levels may be more inhibitory to the synthesis of vitamin K-dependent clotting factors in the elderly than in the young. Excessive and/or erratic ingestion of certain foods rich in vitamin K can diminish the hypoprothrombinemic effect of warfarin, causing warfarin resistance. Examples of vitamin K–rich foods include green leafy vegetables, asparagus, broccoli, cabbage, lettuce, beef liver, spinach, and tomatoes. Although these foods may be used in moderation, vitamin K–poor vegetable substitutes such as beans and potatoes can be offered to the patient as alternatives.

Drug-drug interactions potentiating or inhibiting the effect of warfarin are numerous. Drugs that potentiate the anticoagulant effect include cinemidine, metronidazole, NSAIDs, phenytoin, salicylates, and thyroxine; a
A decrease in warfarin effect occurs with administration of rifampin and barbiturates.\textsuperscript{25}

The platelet inhibitor ticlopidine has not been shown to be more effective than aspirin and has greater toxicity. Possible adverse effects of ticlopidine include diarrhea and neutropenia,\textsuperscript{26} and it has been reported to cause hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura. Caution is recommended. For patients in whom aspirin therapy fails or who are intolerant of aspirin, ticlopidine may be used; however, leukocyte and platelet counts and renal function should be monitored.\textsuperscript{6,26}

### Analgesics

Pain is a common complaint in the elderly, and the importance of pain management to quality of life is becoming increasingly recognized. Acetaminophen appears to be a safe analgesic, although it does not have any anti-inflammatory properties. It may be used in dosages of up to 4 g/day.\textsuperscript{27} At usual dosages (ie, below 4 g/day), acetaminophen does not have adverse gastrointestinal or nephrotoxic effects. Aspirin also may be used for pain relief, but it is well known to cause gastrointestinal hemorrhage, NSAIDs may cause worsened renal function (from decreased renal vasodilation), hyperkalemia, and delirium. It may be ineffective when creatinine clearance is lower than 25 mL/min. Metolazone differs from other thiazides in that it maintains its efficacy despite a creatinine clearance of less than 30 mL/min. Although loop diuretics (eg, furosemide, bumetanide) are preferred when creatinine clearance is low, these are less effective than thiazides in controlling hypertension. Larger doses of loop diuretics are needed in the presence of renal failure. Electrolytes should be monitored periodically when administering diuretics.

### Miscellaneous Agents

#### Antihistamines

Antihistamines such as diphenhydramine, hydroxyzine, and cyproheptadine are best avoided because of their anticholinergic and central nervous system effects. The use of cyproheptadine as an orexigenic agent and diphenhydramine as a hypnotic agent is therefore not recommended.\textsuperscript{7}

#### Iron supplements

These can cause constipation. Dosages greater than 325 mg/day are not necessary; the amount absorbed is not significantly increased\textsuperscript{7} and compliance worsens.

#### H\textsubscript{2}-blockers

H\textsubscript{2}-blockers are often used for prolonged periods for unsubstantiated reasons and tend to cause drug-drug interactions and possible micronutrient deficiencies. Caution should be exercised when prescribing cimetidine in the elderly because it has been associated with mental confusion and disorientation.

### Diuretics

Hydrochlorothiazide, the most commonly prescribed thiazide diuretic, is known to cause hyponatremia, hypokalemia, and delirium. It may be ineffective when creatinine clearance is lower than 25 mL/min. Metolazone differs from other thiazides in that it maintains its efficacy despite a creatinine clearance of less than 30 mL/min. Although loop diuretics (eg, furosemide, bumetanide) are preferred when creatinine clearance is low, these are less effective than thiazides in controlling hypertension. Larger doses of loop diuretics are needed in the presence of renal failure. Electrolytes should be monitored periodically when administering diuretics.

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as they may cause rectal mucosal damage and necrosis. If chronic cathartic use is necessary, sorbitol is well tolerated without long-term effects on the gastrointestinal tract; efficacy is comparable to lactulose.27

Contrast agents. Iodinated compounds are given intravenously, usually for radiologic procedures (eg, angiography, computed tomography scans). Although they are not prescription drugs, they are administered under the guidance of a physician and are associated with nephrotoxicity, particularly in older subjects with diabetes and/or renal insufficiency. Appropriate preparation of high-risk patients by ample hydration has been shown to minimize contrast-induced nephrotoxicity.31 When possible, restrict their use and consider noncontrast alternatives.

Herbal remedies. Use of herbal preparations in the US adult population has increased in recent years, from 33.8% in 1990 to 43.1% in 1997.32 Common remedies include St. John’s wort for depression, gingko biloba for dementia, garlic for hypercholesterolemia, echinacea for respiratory tract infections, and ginger for nausea (and for its antispasmodic effects).32 Bleeding tendencies have been reported in association with use of ginger and garlic. More studies are needed to establish the safety and efficacy of herbal medicines in the elderly.

Grapefruit juice. Grapefruit juice is a known enzyme inhibitor; it contains flavonoids that inhibit the isoenzymes CYP3A4 located in the intestinal mucosa.25 When drugs metabolized by these enzymes are taken with grapefruit juice, the bioavailability improves, increasing effect as well as toxicity. Drugs metabolized by CYP3A4 enzymes include felodipine, nifedipine, quinidine, terfenadine, and triazolam.8

Tobacco smoking, charcoal-broiled meat. These are recognized isoenzyme inducers. Nitrosamines from tobacco and polycyclic aromatic hydrocarbons from charcoal-broiled meat accelerate oxidation of certain drugs (eg, theophylline) metabolized by the CYP system.25

GENERAL RECOMMENDATIONS

PRINCIPLES OF PRESCRIBING

• Know the diagnosis. Obtain a good history from the patient or caregiver along with a complete evaluation. Manifestations of disease in the elderly are often atypical. Resist the urge to treat each symptom with medications; this commonly leads to polypharmacy.

• Conduct a medication review regularly. A patient’s signs or symptoms may be the result of an ADE—consider a drug basis for any new or unexpected symptomatology. Be aware of other simultaneous prescribers who care for the patient. All medications—prescription and over-the-counter—should be listed and reviewed. Discontinue unnecessary drugs. Keep medical records current by listing at each visit all medications taken by the patient. Have a clear therapeutic goal, and make sure prescriptions are consistent with this goal.

• Do not prescribe when in doubt. It is relatively easy to start a patient on medication but harder to discontinue it. Avoid reflex prescribing. Maximize the use of non-pharmacologic interventions (eg, lifestyle modifications). Do not prescribe without an adequate basis or fail to prescribe if needed (eg, for pain or depression).

• Empower patients and caregivers by education. Increase awareness of the physiological changes that occur with normal aging; education lessens anxiety. For example, knowledge of the sleep pattern changes that occur with normal aging may lessen dependence on hypnotics.

• Know well the drugs you prescribe. Know the pharmacokinetics and dynamics of a medication, including possible adverse effects, before prescribing.

• Start low, go slow. This is a dictum mentioned in most literature on pharmacology of aging. Prescribe appropriately, and titrate doses of medications to achieve therapeutic levels while monitoring for clinical response and side effects. Exceptions to low starting doses include antibiotics and antiepileptic agents, which may require a full loading dose to achieve therapeutic levels.

• Be neither the first nor the last to use a new drug. Avoid starting an elderly patient on a new medication whose side-effect profile has not been fully determined. Most research on drug kinetics uses younger subjects. Nevertheless, a truly efficacious and essential drug should not be denied to the patient.

• Write legibly. Prescriptions should be written legibly to avoid errors in interpretation by a physician, nurse, or pharmacist. Written instructions to the patient and/or caregiver should be readable, in large print, and in a language understood by the patient.

COMPLIANCE

Compliance, or adherence, is the extent to which a patient’s behavior regarding drug intake concurs with that of the physician’s instruction.30 Noncompliance occurs in one third to one half of elderly patients.33 Compliance does not change with gender, age per se, or educational attainment. However, noncompliance
increases with the number of medications taken; fur-
thermore, noncompliance may result from additional
concomitant processes such as poor cognition (diffi-
culty understanding instructions), poor vision (diffi-
culty in differentiating medications or reading instruc-
tions), dysphagia (difficulty or inability to swallow large
pills) and impaired hand dexterity (difficulty in self-
administering medications). Other factors that con-
tribute to poor compliance include complex drug reg-
imens, the use of safety closure bottles, long duration
of therapy, and a patient’s belief that the drug may
cause toxicity.Suggestions to improve compliance
include the following:

• **Educate the patient and/or caregiver.** Explain the
  indication and possible side effects for each drug pre-
scribed. Involve the patient and caregivers in the treat-
ment plan by encouraging discussion. Knowledge will
help alleviate anxiety.

• **Simplify the drug regimen.** The fewer the number of
drugs prescribed, the better the compliance. Once-
daily dosing offers the best likelihood of compliance,
followed by twice-daily dosing; more frequent dosing
(3 or 4 times daily) decreases compliance. Alternate-
day dosing can be confusing to older subjects with
impaired memory. An alternative is to use drugs with
extended-release or long-acting forms, if possible.
Decreasing the number of pills per dose has also
been associated with improved compliance. Shorten
the duration of treatment when possible, and tailor
the drug regimen for each indication.

• **Provide clear dosing instructions.** Provide clear and
  simple instructions on dosing, written in large and
  legible print in a language understood by the patient.

• **Encourage use of pillboxes.** Elderly patients may not
  recall when medications should be taken because of
memory impairment. Have the caregiver consider a
weekly pillbox, usually available in the local pharma-
cy, to allocate the medications for better compliance.
Pill cutters are helpful to break medications when
necessary. Because older patients may be handi-
capped by sensory impairment and diminished dex-
terity, child-proof drug containers should be avoided.

• **Consider cost when prescribing.** Try to limit the num-
  ber of prescribed medications. Many older adults
have limited income and may be unable to afford the
out-of-pocket cost of prescription medications.
When possible, settle for generic drugs.

• **Monitor for compliance.** Compliance can be me-
sured directly or indirectly. Determination of drug
concentration in the blood and urine is the most
common direct method. Therapeutic response, self-
reporting, pill counts, and pharmacy records consti-
tute indirect measures. When discussing compliance
with patients, it is important to recognize the diffi-
culty of complete adherence to long-term drug therapy.
Ask non-threatening questions and always be sup-
portive in solving patients’ compliance problems.

**CONCLUSION**

Drug prescribing in the elderly is an art as well as a
science. It requires adequate knowledge of age-related
physiologic changes, an awareness of disease processes,
and an understanding of the altered drug kinetics and
dynamics in the elderly. It is important for health care
providers to follow guidelines for prescribing drugs to
elderly patients, to minimize polypharmacy with its at-
tendant ADEs, and to work closely with patients to en-
hance compliance.

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