



SYMPOSIUM ON GERIATRICS—Part I

Drug Prescribing for Elderly Patients

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- **Objective:** To describe the pharmacokinetic and pharmacodynamic changes that occur with aging and to discuss common problems noted with the use of medications often prescribed for elderly patients.
- **Design:** We searched the medical literature, reviewed pertinent articles, and summarized drug-related information applicable to geriatric patients.
- **Results:** Use of medications is common in the elderly population; most elderly persons take two or more different medications each day. Aging is associated with anatomic and physiologic changes that can have an effect on how medications are handled. Such changes include alterations in various volumes of drug distribution and in drug absorption, metabolism, and clearance. Elderly patients may also have increased or decreased drug effects because of alter-

ation in receptor response. These changes in pharmacokinetics and pharmacodynamics may result in a prolonged drug half-life, an increased potential for drug toxicity, and a greater likelihood for adverse drug reactions.

- **Conclusion:** Medications for elderly patients should be prescribed only after the anatomic and physiologic changes of aging are understood and with increased surveillance for potential drug toxicity or adverse drug reactions.

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ACE = angiotensin-converting enzyme; AV = atrioventricular; CNS = central nervous system; Cr = creatinine; CrCl = creatinine clearance; GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs; $t_{1/2}$ = half-life; Vd = volume of distribution

The population of the United States is growing older every day. Currently, 32 million Americans, approximately 12% of the population, are 65 years of age or older. By the year 2040, that number is expected to increase to 68 million, almost 23% of the projected US population.¹ As a result, the practice of medicine will continue to shift toward the care of elderly patients. In order to make wise treatment decisions when caring for these elderly patients, prevent adverse drug reactions, and improve patient compliance with therapy, an understanding of the physiologic changes that occur with normal aging is of vital importance. Herein we discuss the changes of normal aging as they relate to drug prescribing and offer specific recommendations about drugs that are commonly used in older patients.

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USE OF MEDICATIONS BY THE ELDERLY POPULATION

Elderly Americans spend approximately \$3 billion annually on prescription medications, little of which is reimbursed by third-party payers.² A direct correlation exists between advancing age and the number of drugs prescribed. At least 90% of Americans older than 65 years of age take at least one prescription medication daily, and most take two or more.³ Cardiovascular drugs, antihypertensive agents, analgesics, anti-inflammatory drugs, sedatives, and gastrointestinal (GI) preparations are the most commonly used medications in the geriatric population.⁴ Among institutionalized elderly patients, drug use is even more frequent. In long-term-care facilities, two-thirds of the elderly residents receive three or more drugs daily, and the overall average is seven different medications per resident. Laxatives, analgesics, neuroleptics, and sedative-hypnotics are the most commonly prescribed medications in long-term-care facilities.⁵

Numerous factors contribute to the high prevalence of drug use in the elderly population. The longer one lives, the more chronic medical conditions one accumulates and,

therefore, the more medications are needed to manage them. Many common ailments for which elderly patients seek care have no cure, a situation that often leads to a sense of frustration by both patients and practitioners, along with the patient's expectation that something be done and the physician's perception of a need to do something. All these factors are magnified by the fact that elderly patients often seek medical assistance from several different physicians, sometimes even for the same problem.

The overall effects of a drug depend on the management of the drug by the body (pharmacokinetics) and the target organ sensitivity to the drug (pharmacodynamics). With aging, both of these factors may change by a variety of mechanisms. Generally, the results of these changes in elderly patients are a longer duration of activity, a greater or lesser drug effect, and an increase in the incidence of drug toxicity and adverse drug reactions.⁶ Because of these changes, the benefits of a medication for elderly patients must be carefully weighed against the potential associated risks.

DRUG ABSORPTION

Although few studies have assessed drug absorption in elderly patients, numerous studies have shown reduced absorption of nutrients, such as calcium, thiamine, and iron, with advancing age. The absorption of nutrients, however, often involves active transport, whereas most medications are passively absorbed.

Various anatomic and physiologic changes that occur with normal aging could affect drug absorption. Medications such as ketoconazole, itraconazole, and iron supplements are absorbed better in an acid medium. In general, secretion of gastric acid decreases with advancing age. In addition, elderly persons have a 30% decrease in the mucosal surface area of the small intestine (due to flattening of intestinal villi) and a 40% reduction of blood flow in the small intestine. Despite these age-related changes, no clinically significant decreases in drug absorption attributable to normal aging have been detected.⁷

Conditions that can occur more commonly in the aged population than in young persons—such as various types of malabsorptive states, partial resection of the small bowel, and the concomitant administration of several drugs—have been shown to decrease drug absorption. Antacids, for example, can decrease the absorption of cimetidine, digitalis, tetracycline, phenytoin, iron, quinolones, and ketoconazole. Drugs with anticholinergic activity can slow GI motility and thereby may alter the rate of absorption as well.

DRUG DISTRIBUTION

The duration that a particular drug exerts its effect in an individual patient depends on the volume of distribution

(Vd) of the drug, the metabolism of the drug (primarily by the liver), the clearance of the drug (primarily by the kidneys), or some combination of these factors, all of which change with advancing age. The time needed for a drug to decline to one-half its concentration is known as the drug's biologic half-life ($t_{1/2}$). The $t_{1/2}$ is directly proportional to the Vd and is inversely proportional to clearance of the drug. The Vd of a particular medication is determined by its degree of plasma protein binding and by the patient's body composition.

The composition of the body changes substantially with advancing age. The proportion of adipose tissue increases with aging—from 18% of body mass in young men to 36% in elderly men and from 36% of body mass in young women to 48% in elderly women. This increase in adipose tissue results in a larger Vd for lipid-soluble drugs, causing the $t_{1/2}$ of many lipid-soluble agents to be considerably prolonged in elderly patients. This fact is especially important clinically with drugs that affect the central nervous system (CNS), such as barbiturates and several benzodiazepines.

Between the ages of 20 and 80 years, total body water (both intracellular and extracellular) decreases by as much as 15%. Consequently, the Vd of water-soluble drugs such as lithium and cimetidine is decreased. This reduced Vd can result in an increased serum concentration of water-soluble drugs. When diuretics are used, the extracellular fluid volume can be reduced even further. Ethanol is an example of a water-soluble drug that has an increased effect with advancing age because of a relative increase in drug concentration attributable to a decreased Vd.

Elderly persons have a decreased lean body mass. Digoxin binds to muscle Na^+, K^+ -adenosinetriphosphatase, which decreases because of the reduced muscle mass associated with aging. Consequently, the concentration of digoxin may increase as a result of the decreased Vd. Hence, digoxin toxicity may occur in elderly patients at doses of the drug that are therapeutic for younger patients.

The concentration of plasma proteins such as albumin also tends to decrease in many elderly persons. This change results in a reduced protein-bound (inactive) form of many medications and a greater amount of free (active) drug. Thus, problems can ensue with highly protein-bound medications. Plasma albumin can decrease by at least 15 to 25% because of decreased production by the liver in chronically ill, hospitalized, or institutionalized elderly patients. Therefore, drugs such as digoxin, theophylline, phenytoin, and warfarin can have substantial increases in non-protein-bound levels (and an increased drug effect) during illness. Drugs may also compete for protein-binding sites. A recently added drug can displace a drug that has been in the therapeutic range and thus potentially result in toxicity. α_1 -Acid glycoprotein is an acute-phase reactant that can in-

crease with advancing age in the presence of inflammation (for example, inflammatory arthritis). The result is an increase in the protein binding of basic drugs such as lidocaine and propranolol, which causes a decrease in the amount of unbound active drug.

Of importance, most drug level determinations measure total drug (both protein-bound and free levels). Consequently, measured total drug levels may not accurately reflect drug activity when plasma proteins are decreased;⁸ thus, when possible, a free drug level should be determined if a patient shows signs of toxicity.

DRUG METABOLISM

The rate of drug metabolism by the liver is determined primarily by hepatic function and blood flow. These two factors vary considerably among elderly persons, and no simple method is available to assess the ability of the liver to metabolize drugs in a specific patient. In general, hepatic mass decreases with advancing age, and the number of functioning hepatocytes is reduced.⁹ Hepatic blood flow declines by 0.3 to 1.5% per year. A typical 65-year-old person has a 40 to 45% reduction in hepatic blood flow in comparison with someone who is 25 years old.¹⁰ This physiologic difference results in a major reduction in first-pass metabolism of drugs.

Drugs such as propranolol, lidocaine, calcium channel blockers, and tricyclic antidepressants have a rapid rate of hepatic metabolism. Their rate of metabolism is determined by hepatic blood flow and is said to be "perfusion-limited." Drugs that have limited capacity to be metabolized by the liver, such as warfarin, theophylline, phenytoin, and barbiturates, have a rate of hepatic metabolism determined by enzymatic activity. Therefore, their metabolism is said to be "perfusion-independent." When two perfusion-independent drugs are administered concurrently, the body has a limited capacity to metabolize them, and the metabolism of both proceeds at a slower rate.

Hepatic metabolism occurs by two mechanisms, referred to as phase I and phase II. Phase I metabolism is performed by the microsomal enzyme mixed-function oxidase system (cytochrome P-450) and produces metabolites that may be pharmacologically active. A decline in phase I metabolism is often noted in elderly persons, inasmuch as several of the enzymatic reactions of the P-450 system slow considerably with advancing age.^{11,12} Phase II metabolism involves the conjugation of a drug molecule by glucuronidation, sulfation, or acetylation, usually resulting in a pharmacologically inactive metabolite. Procainamide is metabolized by acetylation. Patients may be fast or slow acetylators. The clinician must depend on trial and error to establish the appropriate dose because fast acetylators cannot be distinguished from slow acetylators. Some patients can be main-

tained on a much smaller dose than others. Phase II metabolism is generally unaffected by aging. Diazepam and alprazolam undergo oxidative (phase I) metabolism, which produces active metabolites, contributing to a prolonged duration of activity in elderly patients. In contrast, lorazepam, oxazepam, and triazolam undergo conjugation (phase II metabolism), which is unaffected by normal aging, does not result in active metabolites, and is not associated with an appreciably increased duration of activity with aging.

DRUG ELIMINATION

Drug elimination is mainly determined by renal function, which, in general, declines steadily with normal aging.¹³ The magnitude of this decline, however, varies greatly among elderly persons and also depends on whether chronic conditions such as hypertension have caused further renal impairment. Overall, renal size, the number of functioning glomeruli, glomerular filtration rate, and renal plasma flow decrease with normal aging.¹⁴ Renal blood flow is reduced by as much as 40% in elderly persons.

Serum creatinine (Cr) is not a reliable indicator of renal function in the elderly population. Cr is a product of muscle breakdown, and because of a decreased muscle mass with aging, production of Cr is reduced. Therefore, one may find a substantial reduction in renal function in an elderly person with a normal serum Cr. The creatinine clearance (CrCl) is a more useful measure of renal function in elderly patients than the serum Cr.¹⁵ The following formula is useful in calculating an estimate of the CrCl:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{Cr}} \times 0.85 \text{ (for females)}$$

For example, a 35-year-old woman who weighs 50 kg and has a serum Cr of 1.0 mg/dL has a CrCl of 62 mL/min, whereas an 85-year-old woman with the same weight and serum Cr concentration has a CrCl of 32 mL/min. When drugs are prescribed that have appreciable renal clearance and a low therapeutic index, such as aminoglycosides, digoxin, procainamide, vancomycin, or lithium, monitoring of the plasma drug level is wise. Pharmacokinetic changes that have been described in elderly patients are summarized in Table 1.

PHARMACODYNAMICS

Changes occur in end-organ responsiveness to medications with aging. These pharmacodynamic changes may be due to a change in receptor binding, a decrease in receptor number, or altered translation of a receptor-initiated cellular response into a biochemical reaction. Pharmacodynamic change is difficult to study; nevertheless, although more is known about pharmacokinetics than about pharmacodynamics in

Table 1.—Physiologic Changes and Reported Pharmacokinetic Changes in Elderly Patients*

Drug factor	Physiologic change	Clinical effect	Example
Absorption	↓ Gastric acidity	↓ Absorption of various drugs	Ketoconazole Itraconazole Ferrous sulfate
Distribution	↓ Small bowel surface area	Clinical relevance unknown	
	↓ Blood flow to small bowel	Clinical relevance unknown	
	↑ Adipose tissue and Vd of lipid-soluble drugs	↑ $t_{1/2}$ of lipid-soluble drugs	Diazepam Flurazepam
	↓ Total body water and Vd of water-soluble drugs	↑ Serum or plasma concentration of water-soluble drugs	Ethanol
	↓ Lean body mass and Vd of drugs bound to muscle	↓ Loading dose required	Digoxin
	↓ Plasma albumin	↓ Protein-bound (inactive) drug (acidic drugs) ↑ Free (active) drug	Phenytoin Warfarin
Metabolism	↑ Plasma α_1 -acid glycoprotein	↑ Protein-bound (inactive) drug (basic drugs) ↓ Free (active) drug	Lidocaine Propranolol
	↓ Phase I hepatic metabolism	↑ $t_{1/2}$ of drugs that undergo phase I metabolism	Diazepam Flurazepam
	Phase II hepatic metabolism unchanged	No change in $t_{1/2}$ of drugs that undergo phase II metabolism	Oxazepam Triazolam
Elimination	↓ RPF and ↓ GFR	↑ $t_{1/2}$ of drugs that undergo renal elimination	Digoxin Gentamicin

*GFR = glomerular filtration rate; RPF = renal plasma flow; $t_{1/2}$ = half-life; Vd = volume of distribution.

elderly patients, specific pharmacodynamic changes have been elucidated for several drugs. A decreased adrenergic receptor response results in less pronounced bradycardia when β -adrenergic blockers are used and less tachycardia when elderly patients receive isoproterenol.¹⁶ In contrast, an increased receptor response is noted with use of benzodiazepines,¹⁷ opiates, or warfarin.¹⁸ Thus, benzodiazepines produce increased sedation, opiates increase the analgesic effect and respiratory suppression, and warfarin enhances the anticoagulant effect in elderly patients. The CNS, bowel, bladder, and heart also seem to be more sensitive to anticholinergic medications. This increased receptor response can result in an augmented drug effect and an increased likelihood of an adverse drug reaction. Pharmacodynamic

changes that have been noted in elderly patients are outlined in Table 2.

ADVERSE DRUG REACTIONS

Adverse reactions to medications are common in the elderly population.⁶ Although changes related to the aging process contribute to adverse drug reactions, elderly patients may be more likely to experience an adverse drug reaction because of increased exposure to medications.¹⁹⁻²² Reducing the number of medications prescribed has been shown to decrease the likelihood of adverse drug reactions.²³ Symptoms frequently attributable to an adverse drug reaction include confusion, nausea, loss of balance, change in bowel pattern, or sedation. These common generic symptoms can be mis-

Table 2.—Physiologic Changes and Reported Pharmacodynamic Changes in Elderly Patients

Physiologic change	Clinical effect	Example
↓ Receptor response	↓ Effect of adrenergic medications	β-Adrenergic agonists β-Adrenergic blockers
↑ Receptor response	↑ Effect of opiates ↑ Effect of benzodiazepines	Morphine Diazepam

taken for other illnesses, and occasionally other medications may even be added to treat these symptoms. This scenario increases the likelihood of an interaction between drugs. The reported incidence of such adverse reactions is 2 to 10% in younger adults and increases to 20 to 25% in elderly patients. An estimated 3 to 10% of all hospital admissions for elderly patients are ascribed to adverse drug effects.²⁴ Advanced age, female gender, lower body weight, hepatic or renal insufficiency, polypharmacy, and a history of prior drug reactions are all associated with an increased risk of adverse drug reactions.

COMMONLY PRESCRIBED DRUGS IN THE ELDERLY POPULATION

The following is a discussion of the various categories of drugs commonly used in elderly patients. Specific medications in each class and potential problems are reviewed.

Cardiovascular and Antihypertensive Agents.

Digoxin.—Digitalis-related toxicity occurs more frequently in elderly than in younger patients and is often difficult to recognize. Classic symptoms of digitalis intoxication, such as nausea, anorexia, and visual disturbances, may occur; however, symptomatic cardiac arrhythmias and conduction disturbances are more common initial manifestations.^{25,26}

The best way to avoid adverse effects of digoxin is to limit its use. Several studies have shown that most patients in normal sinus rhythm have no deleterious effects when use of digoxin is discontinued.²⁷⁻³⁰ Certain patients with atrial fibrillation may not require digitalis therapy. Patients with atrial fibrillation but without a rapid ventricular rate likely have preexisting atrioventricular (AV) node disease, a common occurrence in elderly patients. Because digoxin blocks electrical conduction through the AV node, the addition of digitalis may worsen underlying conduction block. The potential for digoxin toxicity may be enhanced when drugs such as verapamil hydrochloride, amiodarone, or quinidine are used concomitantly.³¹ The Vd for digoxin is reduced in elderly persons because of diminished muscle mass; therefore, the loading dose should be reduced.³² The clearance of

digoxin is delayed when renal insufficiency is present; hence, a reduction in the maintenance dose is needed as well in such patients. Particular caution is necessary when digoxin is used in conjunction with diuretics; this regimen may exacerbate renal impairment and produce hypokalemia, hypomagnesemia, and hypercalcemia, all of which can potentiate digitalis toxicity. Of note, plasma digoxin concentrations do not reliably reflect the level of drug activity. Some elderly patients are more sensitive to the effects of digitalis than others and may exhibit evidence of digitalis toxicity with therapeutic drug concentrations.^{33,34} Electrocardiography is a much better test than determining a digoxin level for detecting digitalis toxicity.

Thiazides.—Thiazides are commonly prescribed as diuretics and antihypertensive agents. Thiazides cause potassium loss in elderly patients and often necessitate potassium supplementation or the addition of a potassium-sparing diuretic. Thiazides may also produce hyponatremia—which, in elderly patients, can result in delirium. Thiazides lose their diuretic effect in the setting of moderate renal insufficiency (CrCl of less than 20 mL/min). They are effective and inexpensive antihypertensive agents and are most useful when administered in low dosage (hydrochlorothiazide, 12.5 to 25 mg/day) because adverse effects are then limited. When thiazides are used in combination with angiotensin-converting enzyme (ACE) inhibitors, antihypertensive activity is enhanced; however, the risk of renal impairment increases. Considerable caution must be exercised when potassium-sparing diuretics are used in association with ACE inhibitors because hyperkalemia may result. Thiazide diuretics can also impair carbohydrate tolerance and can increase uric acid levels. These effects must be considered in patients with diabetes mellitus or gout.

β-Adrenergic Blocking Agents.—β-Adrenergic blocking agents have a diminished effect in elderly patients because of a reduced receptor response.¹⁶ Lipid-soluble β-adrenergic blockers (propranolol and metoprolol tartrate) cross the blood-brain barrier more easily than water-soluble β-adrenergic blockers (atenolol and nadolol) and thus have a greater potential to produce CNS adverse reactions, such as vivid dreams, depression, and fatigue. Cardioselective β-adrenergic blockers (atenolol and metoprolol) have greater affinity for β₁ than β₂ receptors and are less likely to induce bronchospasm. At higher doses, however, this cardioselectivity is lost. These drugs must still be used cautiously in patients with a history of asthma because bronchospasm may occur, even at therapeutic doses. β-Adrenergic blockers with intrinsic sympathomimetic activity (pindolol and acebutolol) are also available. Their use causes less resting bradycardia than traditional β-adrenergic blocking agents.

β-Adrenergic blockers are effective in treating hypertension and are well tolerated by most elderly patients: how-

ever, several potential problems exist when this class of medication is used in the aged. In patients with peripheral arterial disease, symptoms of claudication may worsen because β blockade leaves α receptors, which mediate vasoconstriction, unopposed. Patients with diabetes may also experience problems with use of these agents. Hypoglycemia stimulates the release of epinephrine and results in both α and β receptor stimulation. With β blockade, unopposed α receptor stimulation can result in hypertension with hypoglycemic episodes. In addition, β blockade can prolong the duration of hypoglycemia by inhibiting gluconeogenesis and may also delay the recognition of an insulin reaction by inhibiting the tachycardia associated with hypoglycemic spells.

Calcium Channel Blockers.—Calcium channel blockers are available in three classes: diphenylalkylamines (verapamil hydrochloride), benzothiazepines (diltiazem), and dihydropyridines (nifedipine, felodipine, isradipine, amlodipine besylate, and nicardipine hydrochloride). Although all three classes of calcium channel blockers have the same mechanism of action and all are effective in the treatment of coronary artery disease and hypertension, each class has several unique features. The diphenylalkylamines have the least vascular selectivity. In addition to causing vasodilation, this class has negative inotropic activity and prolongs conduction through the AV node. Verapamil also tends to cause constipation. The benzothiazepines also have effects on cardiac muscle, with effects on the heart similar to those of the diphenylalkylamines but of lesser magnitude. Because of the cardiac effects, these two classes of calcium channel blockers must be used with caution in patients with congestive heart failure or conduction disease. In comparison, the dihydropyridines are much more vascular-specific and, as a result, tend to produce more vasodilation. Adverse effects such as flushing, headache, and peripheral edema tend to be more common with this class of drugs. As a group, the calcium channel blockers tend to be well tolerated by elderly patients; however, the cost of many calcium channel blockers may limit their use in some patients.³⁵ Some of this cost may be offset if one calcium channel blocker can be used to treat more than one problem, such as coexisting hypertension and coronary artery disease.

Psychotropic Drugs. Neuroleptics.—In the past, neuroleptic medications, also known as antipsychotics or major tranquilizers, were used almost exclusively by psychiatrists. Currently, however, primary-care physicians have found that they can be useful in managing behavioral disturbances of patients with dementia. Behaviors such as agitation, aggressiveness, hallucinations, and paranoia often respond to these drugs. The most commonly used neuroleptics belong to one of three classes: phenothiazines (chlorpromazine, thioridazine, and fluphenazine), thio-

xanthenes (thiothixene), and butyrophenones (haloperidol). These medications block CNS neurotransmitters at the postsynaptic membrane. Although these medications are often used interchangeably, they do have different pharmacologic and adverse effects, depending on which neurotransmitters are affected by the drug. Chlorpromazine and thioridazine are α -adrenergic blockers and preferentially block the neurotransmitter norepinephrine. Because of their sedative effects, they are useful for reducing agitated behavior. They also tend to lower blood pressure. As a result, they may worsen preexisting orthostatic hypotension, common in many elderly persons. The α -adrenergic blockers also have anticholinergic effects, which may result in increased confusion, dry mouth, constipation, and urinary retention. Haloperidol and thiothixene predominantly block the neurotransmitter dopamine, tend to be less sedating than the α -adrenergic blockers, and have minimal anticholinergic effects. They tend to cause extrapyramidal symptoms such as restlessness, rigidity, tremor, and motor retardation. Although these adverse effects tend to be related to the dose used, elderly patients are more sensitive to these medications than are younger patients and can have problems even with relatively low doses. Tardive dyskinesia can occur with the use of any neuroleptic medication. Although tardive dyskinesia usually occurs after long-term, high-dose therapy, it can develop in elderly patients with short-term, low-dose use. In some patients, tardive dyskinesia may even develop after use of the medication has been discontinued. Unfortunately, no effective treatment is available. When tardive dyskinesia occurs, the neuroleptic therapy should be discontinued if possible. In most instances, the symptoms will resolve; however, tardive dyskinesia can be irreversible in some patients.

Because of the potential for serious and frequent adverse effects, close follow-up is important in elderly patients receiving neuroleptic medications. Periodically, reduction of the dose or discontinuation of these medications should be attempted. Of importance, although these medications may improve the behavior of patients with dementia, they will not diminish cognitive impairment. Indeed, some patients may even become more confused.

Benzodiazepines.—Up to 40% of prescriptions for benzodiazepines are for patients older than 65 years of age.³⁶ These medications are used primarily for anxiety or insomnia, although they may occasionally be prescribed to reduce agitation in those patients with agitated dementia. Age-related physiologic changes in sleep contribute to the perception of a reduction in the quality and duration of sleep with advancing age. As a result, many elderly patients will request a medication to help them sleep. Although benzodiazepines may offer short-term benefit, they often lose their effect when used on a long-term basis. Many also

have the potential to produce psychologic and physical dependence.

The benzodiazepines can be classified by their $t_{1/2}$ and duration of activity. Long-acting drugs such as diazepam and flurazepam are highly lipid-soluble agents and have a larger Vd. They also have active metabolites. These drugs can accumulate in elderly patients and can cause daytime somnolence, confusion, and an increased risk of falling.^{17,37,38} Intermediate-acting benzodiazepines such as lorazepam and temazepam have a shorter $t_{1/2}$ than diazepam or flurazepam and less tendency to accumulate in elderly patients. Short-acting benzodiazepines such as triazolam and oxazepam have even less tendency to accumulate in elderly persons. Although these medications can be useful in those with transient, short-term insomnia, nightly use of these drugs has minimal benefit for patients with chronic physiologic insomnia. When a medication to induce sleep is thought to be indicated, one might consider the use of antihistamines (for example, diphenhydramine) or low-dose trazodone. These products, however, have their own spectrum of adverse effects. When benzodiazepines are used in the elderly population, long-term daily use and long-acting products should be avoided whenever possible.

Nonsteroidal Anti-Inflammatory Drugs.—For treatment of pain or inflammation, nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for elderly patients. These medications have analgesic, anti-inflammatory, and antipyretic effects. The individual drugs in this class tend to have considerable variation in effects; however, no one nonsteroidal medication has been shown to be clearly superior to another. Elderly patients are more likely to experience adverse effects from NSAIDs than are younger patients.^{39,40} Because an anti-inflammatory effect is often not needed for many rheumatologic conditions in elderly persons, acetaminophen can be effective and much safer. If NSAIDs are thought to be indicated, low doses should be prescribed in those patients with minimal inflammation, in order to minimize adverse drug reactions. (The dose of an NSAID needed for analgesia is lower, in general, than the dose at which anti-inflammatory effects are noted.)

The most common adverse effects of NSAIDs are GI manifestations. Gastric ulceration with occult or overt bleeding is a relatively common occurrence in patients who take NSAIDs on a long-term basis. This result is not due to a local effect on the gastric mucosa but rather a systemic effect on prostaglandin and leukotriene synthesis. Unfortunately, the gastric ulceration and hemorrhage are often not predicted or preceded by dyspepsia, abdominal pain, or nausea. The first symptom of GI toxicity in many elderly patients is upper GI hemorrhage. Nonacetylated NSAIDs (salsalate or choline magnesium trisalicylate) are preferred agents in elderly

patients. These drugs are associated with a lower risk of gastric ulceration than other NSAIDs, although dyspepsia is still common.

NSAIDs also affect other organ systems. Because renal blood flow is highly dependent on prostaglandins, acute tubular necrosis and renal failure may occur with the use of these drugs.⁴¹ NSAIDs also have an antiplatelet effect, similar to aspirin. This effect reverses within 24 to 48 hours after use of the drug has been discontinued (much sooner than aspirin). CNS effects such as confusion can likewise occur with the use of NSAIDs. This effect does not seem to be mediated by prostaglandins.

NSAIDs interact with other commonly prescribed medications. They may increase the serum concentration of digoxin and attenuate the effects of β -adrenergic blockers, ACE inhibitors, and thiazides. The nephrotoxic effects of triamterene are also potentiated by the NSAIDs. Concomitant use can result in severe hyperkalemia.

H₂-Receptor Antagonists.—H₂-receptor histamine antagonists, such as cimetidine, ranitidine, famotidine, and nizatidine, are commonly prescribed in elderly patients. These agents are all well tolerated and are generally equally efficacious in the treatment of peptic ulcer disease, gastroesophageal reflux, and pathologic hypersecretory disorders. Initial duodenal ulcer disease should be treated with short-term, full-dose therapy. Duodenal ulcers tend to heal in 4 to 8 weeks; however, some patients may require long-term maintenance therapy at a reduced dose.⁴² In hypersecretory disorders, such as the Zollinger-Ellison syndrome, H₂-receptor antagonists are considered the preferred therapy over surgical intervention because of the decreased risks involved. H₂-receptor antagonists are also useful in the short-term management of active, benign gastric ulcers. In patients with gastroesophageal reflux disease unresponsive to conventional therapy, relief may be obtained with H₂-receptor antagonist therapy.⁴³ Some evidence suggests that H₂-receptor antagonists have been commonly used for reasons not substantiated in the medical literature and often prescribed for excessively long periods.⁴⁴⁻⁴⁶

Cimetidine was the first H₂-receptor antagonist to be released and is a cytochrome P-450 enzyme inhibitor. It reduces the metabolism of drugs such as phenytoin, carbamazepine, theophylline, warfarin, and quinidine. As a result, the $t_{1/2}$ of these drugs can be increased when they are used in conjunction with cimetidine. Ranitidine has a similar but less effect. Close monitoring and dose adjustment may be necessary. The other H₂-receptor antagonists do not exhibit this enzyme inhibition and thus would not be expected to interact with the previously described medications.

The H₂-receptor antagonists are excreted primarily by the kidneys, and patients with impairment in renal function may have accumulation of the drug. In such patients, dosage

adjustment may be necessary. Concomitant hepatic dysfunction may necessitate further dose adjustment. The H₂-receptor antagonists have a relatively benign adverse reaction profile.⁴⁷ The most common adverse effects include headache, dizziness, and dermatologic reactions. Rare hematologic abnormalities such as leukopenia and anemia have been reported. Cimetidine has also been associated with reversible CNS effects such as confusion, psychosis, and hallucinations—most commonly, in elderly or severely ill patients. These states usually develop within a few days after initiation of therapy and are reversible within a few days after therapy has been discontinued.

CONCLUSION

As a result of age-related physiologic changes and the high frequency of comorbid conditions in this age-group, the appropriate prescribing of medications for elderly patients can be challenging. Polypharmacy is always undesirable. Sometimes, however, use of multiple drugs is unavoidable in the management of patients with several medical problems. The more medications a person takes, the more frequent the dosing, the more complicated the instructions, and the more expensive the medications, the less likely is the patient to take the medications as prescribed. In order to use medications effectively, minimize the likelihood of an adverse drug reaction, and maximize compliance, the following principles should be adhered to when prescriptions are given to elderly patients.

1. Make a diagnosis before drug therapy is initiated. Avoid the tendency to treat symptoms empirically.
2. Carefully weigh the potential benefits of any medication against the risks of an adverse drug reaction. Remember that the risks of an adverse reaction are highest in the elderly population.
3. Begin with low doses of medications if they have potential to cause frequent adverse reactions. Monitor the patient closely for signs of drug toxicity as the medication achieves steady state. Once the medication has reached steady state, gradually increase the dose until the desired effect is achieved.
4. Inquire about the use of over-the-counter medications. Patients often do not realize that such drugs have potential for harm.
5. Periodically review the list of medications used by elderly patients. Occasionally, medications that are intended for temporary use are unintentionally taken for longer periods. Assess for any potential drug-to-drug interactions (which become more likely as the number of medications prescribed increases). Review doses that may need to be adjusted with advancing age.
6. Simplify medication schedules, when possible, to maximize compliance. Aim for once- or twice-daily dosing.

7. Suspect a medication as the cause of any major medical or cognitive change in an elderly patient.
8. Discuss the benefits of the medication with the patient and the consequences of noncompliance.
9. Inform the patient about common potential adverse reactions from a specific medication and what actions to take should they occur.

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