Chapter 5

Susan W. Miller

Therapeutic Drug Monitoring in the Geriatric Patient

The complex process of aging is characterized by progressive loss in the functional capacities of organs, a reduction in mechanisms of homeostasis, and altered response to receptor stimulation.[1] These changes combine to increase the susceptibility of elderly individuals to environmental and physical stressors as well as the effects of medications. The prevalence of diseases increases with advancing age, and this increase is accompanied by an increase in the use of medications.[2] Medication therapy is among the most widely used and highly valued interventions for acute and chronic diseases of older adults, yet the use of drug therapy in the geriatric patient is one of the most difficult aspects of patient care.[3,4] The unexpected or exaggerated response to drug therapy exhibited by a geriatric patient compared with a younger patient of the same sex and body weight can frequently be explained through pharmacokinetic or pharmacodynamic changes.[5] Older patients take more medications than younger persons, yet major drug studies are performed primarily on individuals younger than 55 years of age.

The effects of aging on drug metabolism are complex and difficult to predict. These effects depend on the pathway of drug metabolism in the liver, on environmental factors, and on cardiac function.[6] Although many irreversible changes occur with aging, it is now well recognized that individuals age at different rates (chronological and biological age are not necessarily synonymous). Frailty, a biological syndrome in the geriatric patient, is recognized as a confounding factor when considering the impact of aging on drug disposition.[2,7] The frailty of a geriatric patient can alter drug metabolism, and this effect appears to vary from drug to drug. The frail elderly (those that are vulnerable and are at the highest risk for adverse health outcomes) have been shown to have reduced drug metabolism.[8] Frail older adults are identifiable as those at high risk for dependency, institutionalization, falls, injuries, acute illness, hospitalizations, slow recovery from illness, and mortality.[9] Markers for inflammation, such as tumor necrosis factor [TNF-α], interleukin-6 [IL_6], and C-reactive protein, may serve as biochemical markers for frailty and may prove to be a method to characterize an individual's biological age.[10] Because of the frailty of elderly patients, it is important that the first medication prescribed be the most effective choice for the best chance at an optimal clinical outcome.[11] To make the most effective choice, clinicians should take into consideration both personalized pharmacokinetic changes in drug metabolism and pharmacodynamic responses of individual patients, when selecting drug therapies for geriatric patients.

Pharmacokinetic studies comparing young and older adults are often difficult to accomplish due to the problems associated with recruiting healthy older individuals to compare with healthy younger individuals, however they are increasing in number.[12-28] Problems have been identified with the selection of patient participants and reporting of the results of clinical trials to assess age-related pharmacokinetic differences in drugs.[29] Often, participants are the healthy (younger) geriatrics and not the very old (over the age of 85 and/or frail) geriatric patients. The extrapolation of dosages and possible side effects in the very old population may or may not be appropriate.[29] Physiological differences, pathophysiological changes, altered protein binding, and/or concomitant use of medications may account for the altered pharmacokinetics displayed by older patients.[30]

The following examples illustrate the variability of changes that occur in the elderly. There is evidence to show that increased age may delay absorption of transdermal *opioids*, but not affect the maximum and steady state concentrations. [31] An infusion of morphine into older patients showed a rapid distribution, followed by a slower elimination when compared to younger patients.[32] Recent pharmacokinetic studies have reported no need for dosage changes in the elderly for proton-pump inhibitors, or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors.[33-35] Data shows that the angiotensin converting enzyme inhibitors *trandolapril* and *moexipril* should be initiated at lower doses in geriatric patients, but no overall dosage modifications are necessary.[36] Other data shows that, in the presence of renal impairment, plasma concentrations of ACEIs increase and doses should be adjusted based on renal function.[37] The SERMs (selective estrogen receptor modu-

lators) have variable pharmacokinetic changes associated with aging, with *tamoxifen* and *toremifene* exhibiting increased plasma concentrations with increased age; tamoxifen greater than toremifene; however, neither drug has accompanying package insert recommendation for dosage alterations. No age-related differences in *raloxifene* pharmacokinetics have been identified, but cautionary dosing is advised in both moderate-to-severe renal impairment and in hepatic impairment.[38] Nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit reduced renal clearance in the presence of renal impairment.[39]

Decreased clearance and prolonged half-life of *sertraline* suggest that steady state concentrations would be higher and achieved later during long-term administration to geriatric patients.[40] A reduced clearance for *fosphenytoin*, *ticlopidine*, and *ropinirole* has been shown in geriatric patients, with the clinical significance of this reduced clearance unknown.[41-43] The fluoroquinolone antibacterials, including *ciprofloxacin*, and *levofloxacin* require dosage adjustments based on their predominant renal elimination.[44] The antiepileptic drugs, *felbamate*, *gabapentin*, *lamotrigine*, *levetiracetam*, *oxcarbazepine*, *tiagabine*, and *topiramate,* all exhibit a decrease in apparent oral clearance in elderly patients when compared to non-elderly adult controls.[45] Studies measuring the pharmacokinetics of the cholinesterase inhibitors *tacrine, donepezil, rivastigmine*, and *galantamine* in geriatric patients report some changes in pharmacokinetic parameters, but these are not considered clinically significant and no dosage changes are suggested unless patients are in severe renal impairment (galantamine and creatinine clearance < 9 ml/min).[46] Due to hepatic toxicity, tacrine and galantamine are not recommended for use in patients with severe hepatic impairment.[46]

Information regarding dosage alterations based on the pharmacokinetic profiles of drugs in geriatric patients is very important to the clinician as current dosing in geriatric patients is often based on broad generalizations such as "use one third to one half the usual dose," or anecdotal data—not on solid pharmacokinetic or pharmacodynamic studies. Pharmacokinetic and/or pharmacodynamic differences in older patients may account for either the toxic or subtherapeutic response that often occurs.

Adverse drug reactions or events (ADEs) and drug-drug interactions (DDIs) occur more frequently in geriatric patients, in part because this population is most likely to be using complex drug therapies.[47-53] The estimated annual rate of ADEs for individuals aged 65 years or older has been measured at more than twice the rate for those younger than 65 years of age.[54] Additional data has shown that for persons 65 years of age and older, the estimated annual rate of ADEs requiring hospitalization was nearly seven times the rate for persons younger than 65 years. Although considerable evidence suggests that an ADE will not occur simply because a patient is elderly, pharmacokinetic and pharmacodynamic changes in the elderly may significantly alter drug disposition and must be considered as contributing to ADEs.[55-57] Symptoms of ADEs can be extremely subtle in an elderly patient and may be manifested by increased frequency of falls, increased confusion, excessive sedation, constipation, urinary retention, decreased oral intake, or a general failure to thrive.[58]

Significant ADEs are most likely observed with drugs having a narrow therapeutic index or saturable hepatic metabolism (e.g., *phenytoin*, *warfarin*, and *theophylline*) or when elimination is via a single mechanism or pathway. A study of emergency department visits for ADEs showed that drugs that commonly require regular outpatient monitoring to prevent toxicity (*antidiabetic agents, warfarin, several anticonvulsants, digitalis glycosides, theophylline*, and *lithium*) were involved in the most unintentional overdoses.[54] The patients most at risk usually have multiple disease states or compromised organ function, and they receive multiple drug therapy. Complicated drug therapy, poor compliance, and altered pharmacokinetics are among the many possible causes of ADEs and DDIs.[47,48,52,57-59]

Physiologic Changes

Absorption, distribution, metabolism, and excretion

The processes of absorption, distribution, metabolism, and excretion determine the amount of drug present at any given time within the body's various tissue and fluid compartments.

Pharmacokinetic parameters represent a composite of both genetic and environmental effects.[60-63] The physiologic changes produced by aging that may have important implications for altered pharmacokinetics are summarized in Table 5-1.

Age-related physiologic changes in the gastrointestinal (GI) tract include elevated gastric pH, delayed gastric-emptying, and decreases in GI motility, intestinal blood flow, and absorptive surface area. Reduced gastric secretion of acid can reduce tablet dissolution and decrease the solubility of basic drugs.[64]

Table 5-1. Physiologic Changes with Aging that May Affect Pharmacokinetics[6,62]

Process	Physiologic Effect
Absorption	Reduced gastric acid production Reduced gastric-emptying rate Reduced GI motility Reduced GI blood flow Reduced absorptive surface
Distribution	Decreased total body mass Increased percentage of body fat Decreased percentage of body water Decreased plasma albumin Disease-related increase in alpha-1-acid glycoprotein Altered relative tissue perfusion Altered protein binding
Metabolism	Reduced liver mass Reduced liver blood flow Reduced hepatic metabolic capacity Reduced enzyme activity Reduced enzyme induction
Excretion	Reduced renal blood flow Reduced glomerular filtration Reduced renal tubular secretory function
Tissue sensitivity	Alterations in receptor number Alterations in receptor affinity Alterations in second messenger function[a] Alterations in cellular response Alterations in cellular nuclear response

[a]A chemical (e.g., cyclic AMP or Ca^{++}) inside the postsynaptic neuron released by a first messenger (e.g., a neurotransmitter) and responsible for downstream regulation of a pathway or gene expression.

The delay in gastric emptying allows more contact time in the stomach for

- Potentially ulcerogenic drugs such as the NSAIDs and bisphosphonates.
- Antacid drug interactions due to an increased opportunity for binding.
- Increased absorption of poorly soluble drugs.

A higher incidence of diarrhea and a delay in onset action of weakly basic drugs also result from this physiologic effect.

One study reported a three-fold decrease in *levodopa* availability in the elderly because delayed gastric emptying allowed the increased degradation by GI dopa-decarboxylase to dopamine.[65] Differences in gastric emptying might help explain the unpredictable and inconsistent responses to levodopa in individual patients.[66] The increased degradation of *levodopa* by dopa-decarboxylase occurs when *levodopa* is used alone (not in combination with a dopa-decarboxylase inhibitor such as *carbidopa)*. *Levodopa* is only used in combination therapy as an anti-Parkinson's agent.

Clorazepate, a benzodiazepine, is converted by acid hydrolysis in the GI tract to an active metabolite, desmethyldiazepam. Desmethyldiazepam concentrations have been reported to be lower in both elderly and gastrectomized patients compared with younger adults. This decrease in active metabolite levels is presumed to be a result of a decreased conversion from the parent drug.[67]

Age influences the active transport mechanisms involved in the absorption of nutrients such as sugars, vitamins (e.g., *thiamine* and *folic acid*), and minerals (e.g., *calcium* and *iron*). In elderly patients, this absorption is often reduced.[68] Age-related physiologic changes alone apparently do not influence the passive transport mechanisms by which most drugs are absorbed.

Some drugs with high intrinsic clearance in the liver are metabolized during their passage from the portal vein through the liver to the systemic circulation, thus reducing their oral bioavailability. Drugs with potentially *increased* bioavailability in the elderly, presumably due to a decrease in first-pass metabolism, are shown in Table 5-2.[69,70]

Drugs that undergo first-pass metabolism and may have *decreased* bioavailability in older patients include *clorazepate,*[22] *digoxin*,[71] and *prazosin*.[72] The decrease in bioavailability may be the result of a combination of reduced blood flow to the hepatic system and slowed GI motility that allows for drug degradation in the GI tract prior to absorption.

Although the total amount of absorbed drug reaching the systemic circulation is affected for only a few drugs, age-related physiologic changes can alter the absorption rate, resulting in an erratic and sometimes inconsistent pharmacologic response. The clinical effect of this is a delay in the time to peak or maximum concentration, which is more problematic with therapies where a high peak or short time to peak is important. Clinical factors such as acute congestive heart failure (CHF), achlorhydria, and unusual dietary patterns may occasionally necessitate the intravenous route of administration because of the incomplete absorption via oral and intramuscular routes. The absorption of intramuscularly administered drugs decreases in bedridden elderly patients, perhaps because of changes in regional blood flow. In geriatric patients, percutaneous absorption of transdermal medications can be affected by reductions in the water and lipid layers of the aged skin. Lipophilic medications such as *testosterone*, *estradiol*, and *fentanyl* have shown reduced absorption in geriatric patients.[73] Considerations involved in using controlled-release dosage formulations include age-related changes in GI transit time, motility, and pH.[74]

Binding proteins

Age can alter the distribution of drugs throughout the body and to target organs. Although total protein generally is unaffected by aging, the plasma albumin portion has been shown to decrease from 4 g/dl in young adults to approximately 3.5 g/dl in patients over 80.[75] The mean serum albumin of nursing facility residents has been found to be 3.0 g/dl or lower.[76] The two major plasma proteins to which medications can bind are albumin and alpha-1-acid glycoprotein (AAG), and concentrations of these proteins may change with concurrent pathologies seen with increasing age. Plasma protein binding is a major determinant of drug action, particularly for drugs that are highly protein bound and changes in protein binding can have clinical implications.[30] If albumin is decreased, a compensatory increase in unbound (active) drug occurs if the percentage of the bound drug is 90% or more; however, this is often compensated by increased distribution or clearance, so little or no clinical effect is experienced. In addition to age, disease states such as cirrhosis, renal failure, and malnutrition can lower albumin concentrations.

AAG, an acute phase reactant, binds mostly to lipophilic basic drugs and tends to increase with age and in response to acute illness. The binding of drugs to AAG increases during acute illness and can return to normal after several weeks or months when the acute stress passes and AAG decreases.[77,78] Medications that bind to AAG and are commonly associated with adverse effects in geriatric patients are *lidocaine, meperidine,* and *propranolol*.[30] Though protein binding may be altered in aging, physiological changes and pathophysiological disorders also occur and these changes usually have greater clinical significance than changes in drug plasma protein binding.[30]

Increased unbound (free) fraction

Increases in the free fraction of *naproxen*, *diflunisal*, and *salicylates* have been found in the elderly, presumably as a result of the decrease in albumin protein binding.[79] Increased concentrations of NSAIDs have been associated with a higher incidence of gastric bleeding from peptic ulcers.[80] Whether the increase in gastric bleeding is due to changes in protein binding or the increased drug concentration is not known.

Table 5-2. Drugs with Increased Bioavailability in the Elderly

Amitriptyline	Lidocaine
Chlordiazepoxide	Metoprolol
Cimetidine	Metronidazole
Desipramine	Propranolol
Imipramine	Quinidine
Labetalol	Trazodone
Levodopa	Verapamil

Decreased protein binding (as well as the resultant increased free fraction) is also seen with *phenytoin*, which is cleared from the plasma more rapidly because of an increase in free phenytoin.[81] Seizure control may be seen at lower measured total (bound plus unbound) phenytoin concentrations in the elderly whose unbound fraction has increased. Although the increase in the free fraction of phenytoin with age is statistically significant, it is unlikely to warrant a compensatory change in dose unless the patient has a total phenytoin concentration that is near the upper limit of the therapeutic range and/or that is sufficient to saturate metabolizing enzymes. With *meperidine*, binding to red blood cells decreases with age, thus increasing the amount of free meperidine available in the elderly patient.[82] Meperidine is considered an inappropriate drug for use in the elderly.[83-85]

Although higher concentrations and the resulting therapeutic effects of some drugs may be beneficial, the accompanying risks of toxicity are problematic in the geriatric patient. Doses of most highly protein-bound drugs (>90% protein bound) should be reduced initially and increased slowly if there is evidence of decreased serum albumin (i.e., <3.5 g/dl). If several highly protein-bound drugs are used together, the chance of a drug interaction increases. Table 5-3 shows the impact of age on the protein binding of select drugs.

Lean body weight to fat ratio

Changes in the ratio of lean body weight to fat also can alter drug distribution leading to changes in pharmacologic response. In the average elderly patient, total body water is decreased and total body fat is increased. These changes influence the onset and duration of action of highly tissue-bound drugs (e.g., *digoxin*) and water-soluble drugs (e.g., *alcohol*, *lithium*, and *morphine*). The dosages of most water-soluble drugs are based on estimates of lean or ideal body weight. If a patient's actual weight is less than the estimated lean body weight, the actual weight should be used in most dosage calculations.

Between ages 18 and 85, total body fat increases on average in both females and males; lean body mass eventually decreases in both groups as well. With increasing age, the volume of distribution of lipophilic drugs may increase as a result of diminished protein binding and an increased fat to lean muscle ratio. Fat-soluble drugs (e.g., most *tricyclic antidepressants*, *barbiturates*, *benzodiazepines*, *calcium channel blockers*, and *phenothiazines*) may have a delayed onset of action and can accumulate in adipose tissue, prolonging their action sometimes to the point of toxicity.[86,87] All of these drugs are considered inappropriate in the elderly due to safer alternatives.[83-85]

Drug Elimination

Drugs are primarily cleared from the body by metabolism in the liver, excretion by the kidneys, or some combination of the two processes. A decrease in total body clearance results in higher drug concentrations and an enhanced pharmacologic response, which can lead to toxicity.[86]

Metabolism

For some drugs, hepatic metabolism is highly dependent on blood flow. Liver blood flow can decrease significantly with increasing age and is further compromised in the presence of congestive heart failure (CHF). With drugs that are highly dependent on hepatic metabolism (e.g., most *beta-blockers*, *lidocaine*, and *narcotic analgesics*), a decrease in hepatic clearance can increase the drug concentration and lead to toxicity.

In addition to altering hepatic blood flow, age influences the rate of hepatic clearance by causing changes in the intrinsic activity of selected liver enzymes. This age-related process has been found in the Phase I enzymatic pathway. Common drugs using this pathway and having the potential for metabolism influenced by age include the longer acting benzodiazepines such as *diazepam*, *chlordiazepoxide*, and *clorazepate*. The enzymatic demethylation of *nortriptyline*,[88] *imipramine*,[89] *thioridazine*,[90] and *theophylline* [91] also decreases in the elderly. All of these drugs are considered inappropriate for use in the elderly except *imipramine*.[83-85]

Drugs that undergo hepatic Phase II enzymatic biotransformation (e.g., *lorazepam*, *oxazepam*, and *temazepam*) do not appear to be adversely affected by age; therefore, they are preferred agents for older patients.

At all ages, drug metabolism can be affected by genetics, smoking, diet, gender, comorbid conditions, and concomitant drugs. The cytochrome P (CYP) 450 enzyme system, primarily a part of the Phase I hepatic metabolism pathway, can be affected by many drugs. Of the more than 30 CYP 450 isoenzymes identified to date, the major ones responsible for drug metabolism include CYP3A4, CYP2D6, CYP1A2, and the CYP2C subfamily. Newer evidence in geriatric patients has shown a reduction in CYP2C19 activity, no reduction in

Table 5-3. Effects of Age on Plasma Protein Binding of Select Drugs in Geriatrics

Drugs with decreased protein binding (increased free fraction)

Acetazolamide[b]
Carbenoxolone
Ceftriaxonea
Clomethiazole
Desipramine[a]
Desmethyldiazepam
Diazepam[a]
Diflunisal
Fluphenazine
Flurazepam
Lidocaine[a]
Lorazepama
Meperidine[a,b]
Naproxen
Phenytoin[a]
Salicylate[a]
Temazepam
Theophylline
Tolbutamide
Triazolam[a]
Warfarin[a]

Drugs with increased protein binding (decreased free fraction)

Amitriptyline[a,b]
Benazeprilat
Ceftriaxone[a]
Chlorpromazine[a]
Clomethiazole[a]
Disopyramide[a]
Enalaprilat
Etomidate
Flurazepam
Haloperidol[a]
Ibuprofen[a]
Lidocaine[a]
Naproxen
Nortriptyline[a]
Propranolol[a]

Select drugs with no change in protein binding

Alprazolam
Amitriptyline[a,b]
Atropine
Caffeine
Oxazepam
Chlordiazepoxide
Chloroquine
Desipramine[a]
Desmethyldiazepam
Diazepam[a]
Disopyramide[a]
Donepezil
Etodolac
Fentanyl
Furosemide
Haloperidol[a]
Ibuprofen[a]
Imipramine
Lorazepam[a]
Maprotiline
Meperidine[a,b]
Methadone
Methotrexate
Metoprolol
Midazolam
Nadolol
Nitrazepam[a]
Nortriptyline[a]
Penicillin
Phenobarbital
Phenytoin[a]
Piroxicam
Propranolol[a]
Quinidine
Risperidone
Salicylate[a]
Sotalol
Sulfadiazine
Sulfamethoxazole
Thioridazine[b]
Triazolam[a]
Trimethoprim
Vancomycin
Verapamil
Warfarin[a]

[a]Conflicting data have been reported.
[b]Drugs considered to be inappropriate for use in the elderly.

CYP2D6 activity, and marked variability with little change in the CYP1A2, CYP2C9, CYP2E1, and CYP3A4 isoenzymes.[73,92] CYPs are increasingly being identified in extrahepatic organs such as the intestine, kidney, brain, and skin. The full effect of aging on these enzyme systems is yet to be determined.[93] Unlike renal function, no accurate laboratory tests directly measure liver function for drug dosage adjustment. Nonspecific tests to monitor liver function include ALT, plasma albumin, and prothrombin time.

Renal clearance

Consistent with the behavior of many drugs, pharmacokinetic data from elderly patients are similar to that of patients with mild renal compromise, in that most age-related declines in drug clearance can be explained by reductions in renal function.[94] Age-related physiologic changes in the kidneys influence drug response and elimination more than hepatic changes in the geriatric patient. Between ages 20 and 90, the glomerular filtration rate (GFR) may decrease as much as 50% (average decline of 35%). The average CrCl of elderly nursing facility residents has been found to be about 40 ml/min.[95] Serum creatinine is frequently used to monitor kidney function, but this test alone is of limited utility in estimating the GFR of the geriatric patient. Serum creatinine does not increase significantly unless kidney function deteriorates greatly. The production of creatinine, which is dependent on muscle mass, decreases in the elderly; therefore, an apparently normal serum creatinine in a geriatric patient may not be a valid predictor of renal function and drug elimination. Blood urea nitrogen (BUN) also is not a useful predictor of renal function because it can be affected by hydration status, diet, and blood loss.

The most accurate, readily available estimation of GFR in the elderly is creatinine clearance (CrCl), which correlates well with both GFR and tubular secretion. The CrCl can be estimated using a standard equation that considers age, body weight, and serum creatinine in patients with stable renal function (see Chapter 1). Of course, mathematical equations are simply estimates of an individual's actual renal function. Even the best methods for estimating creatinine clearance may result in suboptimal dosing for many elderly patients. For geriatric patients with low serum creatinine <1.0 mg/dl, (88.4 µM/L SI), the practice of rounding the serum creatinine to 1.0 mg/dl (88.4 µM/L SI) may result in underestimation of creatinine clearance and suboptimal dosing.[96]

Dosages of drugs that are primarily renally excreted should generally be adjusted if the patient has lost more than 50% of kidney function. If creatinine clearance is less than 50 ml/min, major dosage adjustments may be necessary to avoid drug toxicity. Some common drugs with a narrow therapeutic range that are excreted primarily unchanged by the kidneys are shown in Table 5-4.

Age-Related Pharmacodynamic Changes Influencing Drug Response

With increasing age, the tolerance to drugs decreases as a result of altered pharmacodynamic responses at target organs. Pharmacodynamics governs the type, intensity, and duration of drug action. The clinical manifestation of this altered sensitivity may range from an insignificant response, to an adverse drug reaction, or to therapy failure.

Table 5-4. Select Narrow Therapeutic Range Drugs with Primary Renal Excretion

Acetazolamide[a]	H2-antagonists (e.g., cimetidine)
ACE inhibitors	Lithium
Amantadine	Methotrexate
Aminoglycosides	Penicillin
Cephalosporins	Procainamide
Chlorpropamide[a]	Quinidine
Digoxin	Tetracycline
Disopyramide[a]	Vancomycin
Ethambutol	

[a]These drugs are considered inappropriate for use in the elderly.

Qualitative differences in drug response also may occur. Pharmacodynamic alterations are often unpredictable and can lead to toxicity. Altered response may be due to changes in receptor number or affinity, depletion of neurotransmitters, disease, or physiologic changes. With aging, there is evidence of:

- Decreased acetylcholine, dopamine, and serotonin
- Decreased enzymatic degradation of monoamine oxidase
- Impaired baroreceptor response to blood pressure changes
- Decreased responsiveness of beta-adrenergic receptors
- Increased pain tolerance
- Decreased antibody response to vaccination
- Decreased *insulin* sensitivity
- Decreased cortisol suppression
- Enhanced responsiveness to the anticoagulants *warfarin* and *heparin*
- Enhanced responsiveness to thrombolytics

Altered end organ sensitivity may result in exaggerated pharmacologic response, as seen with *barbiturates* and *benzodiazepines*, or diminished pharmacologic response, as seen with *beta-blockers*, *beta-agonists*, and *calcium channel blockers*. Other affected drug classes include the *narcotic analgesics*, *antihypertensive agents*, *antiparkinson drugs*, *phenothiazines*, and *antidepressants.* The incidence and irreversibility of tardive dyskinesia are increased in the elderly and may be due to age-related imbalances in neurotransmitters.[97]

Dosing adjustments are usually necessary since many of these same drugs are also influenced by age-related physiologic changes, especially drug distribution and elimination. The net effect in an individual patient is often difficult to predict. For example, elderly patients have increased bioavailability of *beta-blockers* but decreased responsiveness at the receptor site level (a variable effect is seen with *propranolol*). Another example is that *theophylline's* inotropic effect increases with age but its bronchodilator effect decreases.[98] Drugs that may exhibit an increased pharmacologic response in the geriatric population include *halothane, hydroxyzine*, *metoclopramide, warfarin*, and the *calcium channel blockers*.[98] Age related peripheral and central pharmacokinetic changes may contribute to age-related sensitivity to *antipsychotic agents*, but pharmacodynamic mechanisms may play the most significant role in a geriatric patient's response to any dose of an antipsychotic agent.[99]

More than one in six elderly patients is taking prescription drugs that are not suited for geriatric patients and may lead to physical or mental deterioration and possibly death.[100] Recently strategies have been developed in attempts to foster appropriate prescribing of medications in the geriatric population overall. The explicit criteria for determining potentially inappropriate medication use by elderly patients, labeled the "Beers Criteria," were originally published in 1992, and have since been twice updated.[83-85] These criteria are listed in Table 5-5.

These criteria were developed through a consensus panel of experts in geriatric care, geriatric pharmacology, geriatric psychopharmacology, and nursing home care. These experts reached agreement on criteria defining inappropriate drug use in nursing home residents. The criteria relate to certain drugs that should not be used and doses and durations of therapy of some drugs that should not be exceeded in the older patient who is a resident of a nursing facility.[84] These criteria have since been applied and evaluated in geriatric patients in various levels of care, including assisted living facilities, community dwelling, receiving care from office-based physician practices, and emergency departments.[101-108]

A study of use of these medications in a very large group of hospitalized senior patients showed that about half of geriatric patients received a medication deemed inappropriate according to Beers List criteria.[109] Practitioners may extrapolate these recommendations to the geriatric patient population at large, keeping in mind that they are not meant to regulate practice in a manner to which they supersede the clinical judgment and assessment of the practitioner.[85] Refined Beers Criteria to include preferred medications for use in geriatric patients, or those with the greatest benefit-to-risk ratio for use in geriatric patients, are in development.[110]

Summary of Changes

Table 5-6 is a compilation of the pharmacokinetic and pharmacodynamic literature available on the dosing of drugs in the geriatric population. However, dosing of any drug in a specific patient should be based on that patient's response and ability to clear the drug.[111-112]

Table 5-5. Explicit Criteria for Inappropriate Medication Orders[83-85]

Medications that should (generally) be avoided in geriatric patients

- Sedative or hypnotic agents
  - Long-acting benzodiazepines
    - Chlorazepate
    - Chlordiazepoxide
    - Diazepam
    - Flurazepam
    - Quazepam
    - Meprobamate
  - Short-acting benzodiazepines
    - Alprazolam
    - Lorazepam
    - Oxazepam
    - Temazepam
    - Triazolam
- Antidepressants
  - Amitriptyline
  - Combination antidepressants-antipsychotics
  - Doxepin
  - Fluoxetine (daily)
- Antihypertensive agents
  - Clonidine
  - Doxazosin
  - Ethacrynic acid
  - Guanethidine
  - Hydrochlorothiazide
  - Methyldopa
  - Nifedipine (short-acting)
  - Reserpine
- Nonsteroidal anti-inflammatory drugs
  - Indomethacin
  - Ketorolac
- Oral hypoglycemic agents
  - Chlorpropamide
- Analgesic agents
  - Propoxyphene (single product and combination)[a]
  - Pentazocine
  - Meperidine
- Platelet inhibitors
  - Dipyridamole (short-acting)
  - Ticlopidine
- Muscle relaxants or antispasmodic agents
  - Carisoprodol
  - Chlorzoxazone
  - Cyclobenzaprine
  - Methocarbamol
  - Metaxalone
  - Orphenadrine
  - Oxybutynin

Table 5-5. (Continued)

Gastrointestinal antispasmodic agents
Dicyclomine
Belladonna alkaloids combination
Thioridazine
Digoxin
Cimetidine
Ferrous sulfate (greater than 325 mg/day)
Trimethobenzamide
Antiarrhythmics
Disopyramide
Amiodarone
Anticholinergics and antihistamines
Chlorpheniramine
Cyproheptadine
Dexchlorpheniramine
Diphenhydramine
Hydroxyzine
Promethazine
Tripelennamine
All barbiturates (except phenobarbital)
Amphetamines and anorexic agents
Long-term use of full-dosage, longer half-life non-COX-selective NSAIDs
Naproxen
Oxaprozin
Long-term use of stimulant laxatives
Bisacodyl
Cascara sagrada
Neoloid (except in the presence of opiate analgesic use)
Nitrofurantoin
Methyltestosterone
Mineral oil
Desiccated thyroid
Estrogens (not in combination with progestins)

[a]Withdrawn from the U.S. market in November 2010.

Table 5-6. Pharmacokinetic Parameters and Average Doses of Drugs Commonly Used in Geriatric Patients[a,110,11]

Drug	Volume of Distribution	Clearance	Half-Life	PB (%f)	Time to Peak	Dynamics	Dose (mg/day)	Comment
Acarbose		D					75-300	Avoid use in CrCl >2 ml/min
Acetaminophen	D	D	I		D		1500–3000	Hepatic metabolism not significantly altered; no dosage adjustment necessary unless patient is taking chronic high doses
Alendronate	D						10	No dosage adjustment necessary in elderly; use not recommended in CrCl < 35 ml/min
Alprazolam	D	D	I	NC	D	**	0.75–2	
Amantadine	D		I				200	Dosage reduction in renal impairment
							CrCl (ml/min/1.73 m^2)	Dose
							≥80	100 mg twice daily
							60–79	200 mg/100 mg on alternate days
							40–59	100 mg once daily
							30–39	200 mg twice weekly
							20–29	100 mg three times weekly
							10–19	200 mg/100 mg alternating every 7 days
Amikacin	I	D	I				***	Dose conservatively based on CrCl
Aminophylline	I	NC	I	NC			0.4 mg/kg/hr	
Amitriptyline	I	D	I	D*	I		10–150	Prolonged half-life; evaluation of therapeutic effect to be delayed; increased bioavailability
Amlodipine	NC	D	I			**	2.5–10	Elderly may experience greater hypotensive response
Amoxicillin							750–1500	Dosage reduction in moderate to severe renal impairment
Ampicillin	NC	D	I		I		500–2000	Dosage reduction in moderate to severe renal impairment
Aripiprazole							7.5–30	Dosage adjustments not routinely indicated on basis of age, gender, race, or renal or hepatic impairment status
Aspirin	I	D	I	I*	I		1300–4000	
Atenolol	I	D	I				25–150	
Azathioprine	No data	D	I	I	No data		1.5–2.5	If CrCl <50ml/min give 75% of dose; if CrCl < 10 ml/min, give 50% of dose

Table 5-6. (Continued)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%f)	Time to Peak	Dynamics	Dose (mg/day)	Comment
Azithromycin	NC	NC	NC	NC	No data		250-500	If CrCl < 10 ml/min, use with caution
Benazepril	NC	I	NC	NC	Exaggerated		5–40	Preferred class in comorbid CHF, DM, HTN
Bleomycin	NC	*	I	*				If CrCl <50 ml/min give 75% of dose; if CrCl < 10 ml/min, give 50% of dose
Bupropion		D					100–300	SE profile allows use in patients intolerable to TCAs. A single and multiple dose pharmacokinetic study suggested that accumulation of bupropion and its metabolites may occur in the elderly.
Buspirone	NC	D	I	NC	NC	I	10–60	Slow titration to avoid side effects in hepatic failure; reduced sedation advantageous
Busulfan	NC			D				
Candesartan							8–32	Use lower doses in mildly impaired hepatic and renal function; stronger effect on blood pressure at any dose
Captopril		D	I			I	12.5–250	In renal impairment monitor K+; see benazepril
Cefadroxil			I	NC	NC		1–2 g/day	Base dose on renal function and severity of infection
Cefaclor	NC	D	I	NC	NC		750–1500	If CrCl <50 ml/min, use 50% of dose twice daily
Cefamandole	NC	D	I	NC	NC		4–12 g/day	If CrCl <50 ml/min, reduce dose and increase dosage interval
Cefazolin	NC	D	I					Dosage reduction in renal impairment; all adults receive loading dose of 500 mg
							CrCl (ml/min)	Dose
							≥55	Usual adult dose
							35–54	Usual adult dose every 8 hr
							11–34	One-half usual adult dose every 12 hr
							≤10	One-half usual adult dose every 18–24 hr
Cefdinir	NC	NC	NC	NC	NC		300–600	Reduce dose by 50% in renal impairment
Cefepime	NC	D	I	NC	NC		0.5–4 g/day	Base dose on renal function and severity of infection
Cefixime	NC	D	I	NC	NC		400	If CrCl 21–60 ml/min, give 75% of usual dose; < 20 give 50%

Cefoperazone	NC	D	I	NC	NC	2–12 g/day	Reduce dose in hepatic failure; sodium content is 1 g (1.5 mEq)
Cefotaxime	I	D	I	NC	NC	2–12 g/day	If CrCl = 10–50 ml/min, give every 8–12 hr; if < 10 mg/min, give every 24 hr; a significantly greater increase in t ½ and decrease in CL is reported in patients > 80 years of age
Cefotetan	NC	D	I	NC	NC	1–6 g/day	If CrCl <30 ml/min, increase dosing interval
Cefoxitin	I	I	I	D		3–8 g/day	Dosage reduction in severe renal impairment (may need to give every 12–48 hr)
Cefpodoxime	NC	D	I	NC	NC	200–800	If CrCl <30 ml/min, give every 24 hr
Cefprozil	I	D	I	NC	NC	500–1000	Administer for ≥10 days
Ceftazidime	D	D	I	D	NC	*	*Base on renal function; minimum interval is 12 hr
Ceftizoxime	I	D	I	NC	NC	1.5–12 g/day	If CrCl <80, reduce dose
Ceftriaxone	D	D	I	I		500–2000	No dosage reduction with impaired renal or hepatic dysfunction; in severe renal impairment or in both hepatic and substantial renal impairment (maximum dosage of 2 g daily)
Cefuroxime	NC	D	I	NC	NC	0:250 mg–1 g/day P: 3–6 g/day	If CrCl <20 ml/min, reduce dose
Celecoxib						200–400	Use lowest recommended dose in patients weighing <50 kg
Cephalothin	I	D	I		I	3–6 g/day	Dosage reduction with concurrent renal and hepatic dysfunction
						CrCl (ml/min)	Dose
						>50–80	2 g every 6 hr
						>25–50	1.5 g every 6 hr
						>10–25	1 g every 6 hr
						2–10	500 mg every 8 hr
Cephradine							Dose based on degree of renal impairment, severity of infection, and susceptibility of causative organism
						CrCl (ml/min)	Dose
						>20	500 mg every 6 hr
						5–20	250 mg every 6 hr

Table 5-6. (Continued)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%f)	Time to Peak	Dynamics	Dose (mg/day)	Comment
							<5	250 mg every 6 hr
Chlorambucil	NC	*	*	*	*			
Chlordiazepoxide	I	D	I	NC*			10–40	Not a drug of first choice in the elderly
Chlorpromazine	I	D	I	D			10–800	
Chlorpropamide							100–750	Inactive metabolite excreted via urine; avoid in elderly
Cholestyramine	Not absorbed*	*	*	*	*		16–24 g/day	
Cimetidine	D	D	I				300–600	If CrCl <30 ml/min/1.73 m^2, 300 mg every 12 hr (intravenous or oral); further dosage reduction in concomitant hepatic impairment. Half-life dependent on urine pH
Ciprofloxacin		D	I					If CrCl = 30–50 ml/min/1.73 m^2, 250–500 mg every 12 hr (intravenous or oral); if CrCl = 2–25 ml/min/1.73 m^2, 250–500 mg (oral) every 18 hr or 200–400 mg every 24 hr
Cisapride	NC	NC	NC	NC	NC		40–80	Css higher, no clinical effect; use restricted due to QTc/ Torsade de Pointe
Cisplatin	*	*	*	*	*			Hydrate to prevent toxicity. If CrCl <50 ml/min, give 75% of dose; if CrCl < 10 ml/min, give 50% of dose
Citalopram	*	D	I	*	I		20–40	Avoid in CrCl < 20 ml/min
Clarithromycin							500 - 1000	If CrCl < 30 ml/min, give 50% of dose or every 24 hrs
Clonidine		D					0.1–1.2	Potential for adverse CNS effects
Colestipol	Not absorbed*	*	*	*	*		13–30 g/day	
Clorazepate	I	D	I	I	I	**	15–30	
Cyclophosphamide	I	D	I			**		If CrCl < 10 ml/min, give 75% of dose; risk of hemorrhagic cystitis
Daunorubicin	*	*	*	*	*			
Desipramine		I	I*				20–150	Prolonged half-life; evaluation of therapeutic effect to be delayed
Diazepam	I	D	I	I*		**	2–20	
Diclofenac	NC	NC	NC	NC	NC		50–150	High risk for GI bleed or CNS effects; reduce dose in CrCl <50 ml/min

Diflunisal	NC	D	I	NC	NC		500–1500	High risk for GI bleed or CNS effects
Digoxin	D	D	I				0.125–0.25	Conservative dosing based on IBW and CrCl
Diltiazem	NC	D	I			**	120–480	Initiation with low dose because of significantly reduced clearance; see amlodipine
Diphenhydramine	NC	D	I				25–50	Elderly more sensitive to anti-cholinergic and sedative effects
Donepezil	I	NC	I					No dosage adjustments suggested
Doxepin			I				25–150	Prolonged half-life; evaluation of therapeutic effect to be delayed
Doxorubicin	NC	NC	NC	NC	NC			Risk of acute renal failure and nephritic syndrome
Doxycycline	NC	D	I				50–100	Tetracycline drug of choice in severe renal impairment
Enalapril	D	D	I				2.5–40	See benazepril
Erythromycin		D	I				1–4 g/day	
Eplerenone							50–100	
Eprosartan							400–800	Monitor BP and volume status
Escitalopram			I				10	34% increase in maximum concentration; 50% increase in AUC
Esomeprazole	NC	NC	NC		NC		20–40	No dosage adjustment in renal insufficiency or mild to moderate hepatic dysfunction; maximum dose of 20 mg in severe hepatic dysfunction
Ethanol	D							Increased concentrations due to lowered volume of distribution; additive effects with other sedatives
Etodolac	NC	NC	NC	NC	NC		400	High risk for GI bleed or CNS effects
Ezetimibe							10	Plasma concentrations higher in geriatric patients in multiple-dose study Bioavailability increased in severe renal and hepatic impairment
Famotidine							CrCl (ml/min)	Dose
							>60	Usual adult dose 40 mg
							30–60	20 mg
							<30	10 mg
							<10 mg	4 mg

Table 5-6. (Continued)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%f)	Time to Peak	Dynamics	Dose (mg/day)	Comment
Fentanyl		D	I		?	I		Increased age may delay absorption from transdermal system
Felodipine						**	2.5–10	In hepatic impairment, use initial dose of 2.5 mg/day; avoid doses >10 mg/day; see amlodipine
Fenoprofen	NC	NC	NC	NC	NC		1.2–4 g/day	High risk for GI bleed or CNS effects
Fexofenadine			I				60–180	Peak plasma concentrations 99% higher in elderly; however, no adverse effects observed
Fluorouracil	NC	NC	NC	NC	NC			
Fluoxetine							20–40	SE profile allows use in patients who can't tolerate TCAs
Flurazepam				I		**	15	Dose-related drowsiness from drug accumulation
Flurbiprofen	NC	NC	NC	NC	NC		200–300	High risk for GI bleed or CNS effects
Flutamide	*	*	*	*	*		450	Gynecomastia; antiandrogenic
Fluvastatin	NC	NC	NC	NC	NC		2–10	No dosage reduction in reduced CrCl
Fosphenytoin	NC	D						Lower and less frequent dosing required
Fosinopril							5–40	See benazepril
Furosemide	D	D	I	NC		**	40–2000	
Gabapentin		D						Dosage reduction in renal impairment; base dose on calculated CrCl
							CrCl (ml/min)	Dose
							30–60	200–700 twice daily
							16–29	200–700 daily
							15	100-300 daily
							<15	Dose appropriately
Gatifloxacin		D	I	I	NC	I	200–400	Dose-dependent QT prolongation; assess renal function
Gemfibrozil		NC	NC	NC			1200	
Gentamicin	I	D	I			**		Conservative dosing based on weight and CrCl; interpatient variation
Glimepiride						**	1–8	Rapid and prolonged hypoglycemia >12 hr reported

Glipizide		NC	NC				5–40	Inactive metabolite excreted via urine
Glyburide	I	NC	I				2.5–20	Reduce dose in CrCl <10 ml/min/1.73 m^2
Haloperidol			I	D*			0.25–4.0	Elderly more susceptible to side effects; prolonged half-life
Heparin						**		Increased age may increase risk of major bleeding
Hydralazine						**	20–200	
Hydrochlorothiazide		I					25–50	Not effective in CrCl<30 ml/min
Hydrocodone	I	D	I	NC	NC	I	10–30	Enhanced CNS effects and constipation noted
Hydroxyurea		*	*	*	*			If CrCl <50 ml/min give 50% of dose; if CrCl < 10 mg/min, give 20% of dose
Ibuprofen	NC	NC, D	NC	NC	NC		800–3200	High risk for GI bleed or CNS effects
Imipramine			I	NC			30–150	Prolonged half-life; evaluation of therapeutic effect to be delayed
Indomethacin			I				50–200	Other NSAIDs preferable due to efficacy and lower toxicity
Isrbesartan							150–300	See eprosartan
Isoniazid	D	D					200–300	Dosage adjustment in slow acetylator patients
Isradipine						**	5–10	See amlodipine
Ketoprofen	I	D	I				150–300	
Ketorolac	NC	D	I	NC	NC		60–120	High risk for GI bleed or CNS effects; reduce dose because of decreased clearance
Labetalol		D	I				200–2400	Initiation with lower doses because of increased bioavailability with age
Lamotrigine		*					100-500	If CrCl 10–50 ml/min give 75% of dose; if CrCl < 10 mg/min, give 100 mg every other day
Lansoprazole		D	I				15–30	No dosage reduction in reduced CrCl
Levetiracetam							1000–3000	Essential to base dose on calculated CrCl
							O/P	
							CrCl (ml/min)	
							50–80	
							30–50	
							<30	

Table 5-6. (Continued)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%f)	Time to Peak	Dynamics	Dose (mg/day)	Comment
Levodopa	D	D	D		I			Decreased bioavailability possibly due to slowed gastric emptying
Levofloxacin		D	I				250–500	Dosage reduction based on renal impairment. If CrCl = 20–49 ml/min/1.73 m^2, 250 mg every 24 hr (after initial dose of 500 mg). If CrCl 10–19 ml/ min/1.73 m^2, 250 mg every 48 hr (after initial dose of 250 mg for renal infections and 500 mg for others)
Lidocaine	I	D	I	D		**		Decreased clearance in presence of CHF or liver disease
Lisinopril		D	I				2.5–40	See benazepril
Lithium		D	I				150–900	One-half initial dose because of susceptibility to volume depletion; dose based on drug concentrations (0.4–0.7 mEq/L)
Loratadine			*				10	Wide variation in half-life is a consideration in initiating dosing
Lorazepam	D	D	I	I*	**		1–3	
Losartan			I				25–100	See eprosartan
Maprotiline							25–75	
Lovastatin		NC	NC	NC			20–80	
Meclofenamic acid		NC	NC	NC	NC		150–400	High risk for GI bleed or CNS effects
Mefenamic acid		NC	NC	NC			1000	High risk for GI bleed or CNS effects
Melphalan		D	I				6	If CrCl <50 ml/min, give 75% of dose; if CrCl < 10 ml/min, give 50% of dose
Meperidine	I	D	I	I*		**	150–500	Dosage reduction because of increased sensitivity; elderly more susceptible to side effects
Metformin		D	I				850–2500	Lower dosages and frequent monitoring are recommended
Methotrexate	NC	D	I	NC	NC		5–10 mg/week	For rheumatoid arthritis; if CrCl <50 ml/min, give 50% of dose; if CrCl < 10 ml/min, avoid; refer to specific disease protocols for neoplastic disease
Methyldopa		D	I				250–3000	May be inappropriate due to side effect profile
Metoclopramide	NC	D	I	I	NC	I	0:10–20 P:10–20	Geriatrics more likely to develop dyskinesias

Metoprolol		NC, I	NC, I	NC	D		25–300	
Miglitol							75–300	
Mirtazapine		D	I			I	15–45	Dosage reduction in mild to moderate hepatic and renal impairment
Misoprostol			I				0.1–0.4	Routine use as prophylaxis not justified
Moexipril	I				I		3.75–30	Initiate at lower dose; no overall reduction in total daily dose
Morphine	D	D	D				20–100	Dosage reduction because of increased sensitivity; elderly more susceptible to side effects
Moxifloxacin	NC	NC	NC	NC	NC		400	
Nabumetone	NC	NC	NC	NC	NC		1–2 g/day	High risk for GI bleed or CNS effects; reduce dose if CrCl <50 ml/min
Nadolol				NC			40–320	
Naproxen	I	D	I	I	I		500–750	Avoid use in CrCl <30
Nateglinide	No data						60–360	
Nefazodone	NC	D	I	NC	NC	–	100–400	Conflicting pharmacokinetic data reported in single-dose vs. multiple-dose studies
Nicardipine	NC	D	NC				30–60	See amlodipine
Nifedipine	NC	D	I			**	30–120	See amlodipine
Nisoldipine		D	I			**	10–40	See amlodipine
Nitroglycerine	I		I			Exaggerated		Pharmacokinetics independent of age. Increased sensitivity to drug requires lower dosages
Nizatidine	NC	D	I			Exaggerated	150–300	
Nortriptyline	I	D	I	D*			10–50	Prolonged half-life; evaluation of therapeutic effect to be delayed
Olanzapine	NC	D	I		NC		2.5–10	
Olmesartan							20–40	For patients with possible depletion of intravascular volume (diuretic therapy or impaired renal function), initiate under close supervision and consider using a lower starting dose.
Omeprazole		D	I				20–40	Bioavailability slightly increased; however, no dosage adjustment required. No dosage reduction in reduced CrCl
Oxaprozin	NC	NC	D*	NC	NC		1200	Dual elimination (renal and hepatic) leads to decreased t ½ in chronic dosing; high risk for GI bleed or CNS effects

Table 5-6. (Continued)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%f)	Time to Peak	Dynamics	Dose (mg/day)	Comment
Oxazepam	I	D	I	NC	I	**	10–60	
Oxybutynin	NC	NC	I	NC	NC	NC	5–15	Lower doses improve tolerability
Oxycodone	I	D	I	I	NC	I	10–20	Enhanced CNS effects and constipation noted
Pantoprazole							40	No dosage adjustment required in elderly
Paroxetine	D		I				10–40	See fluoxetine; half-life and steady-state concentration increase disproportionately to dose with single and multiple dosing
Penicillin G			I	NC			1–2 g/day	Dosage reduction in moderate to severe renal impairment
Perindopril							4–8	See benazepril
Phenobarbital		D	I	NC			30–60	Dose administration at bedtime to avoid excessive sedation; tolerance within a few weeks
Phenytoin		D	I*				200–300	Decreased serum albumin concentrations may increase clearance; monitoring of free phenytoin concentrations
Pioglitazone	*	*	*	*	*		15–15	No dosage adjustment required
Piroxicam	D	D	I	NC	D		10–20	Avoid due to long half-life (60–70 hr) and higher GI bleed risk
Pravastatin	NC	NC	NC	NC			10–40	
Prazosin	I	D	I				2–10	
Probucol	*	*	*	*	*		1000	
Propoxyphene	NC	D	I	I	NC		*65 (100)	Not recommended in geriatrics
Propranolol	D	D	I	D*		**	40–480	
Quetiapine		D					25–200	Use 40% to 80% lower doses in elderly as compared to younger patients
Quinapril			I				2.5–80	See benazepril
Quinidine		D	I	NC			600–3600	Dosage reduction because of decreased clearance; dose based on side effects, therapeutic response, and concentrations (2–6 mg/L)
Rabeprazole							20	No dosage adjustment necessary
Raloxifene	NC	NC	NC				60	No dosage adjustment necessary
Ramipril							1.25–20	See benazepril

Ranitidine	D	D	I		NC		150–300	Prolonged half-life; if CrCl <50 ml/min, 150 mg every 24 hr orally or 50 mg every 18–24 hr intramuscularly or by intravenous intermittent slow infusion or direct injection
Repaglinide							1–16	Has not been studied extensively in the elderly
Risedronate							5	Not recommended for use in severe renal impairment (CrCl <30 ml/min). No dosage adjustment necessary in CrCl at least 30 ml/min or in elderly
Risperidone	NC	D	I	I	NC		0.5–2	Titrate slowly to avoid ADRs
Rivastigmine			I				3–12	Titrate dose to tolerance
Ropinirole	NC	D	I				0.75–24	Slow titration dose required; clinical significance of reduced clearance unknown
Rosiglitazone	*	*	*	*	*		4–8	No dosage adjustment
Sertraline	D	D	I	I			25–50	See fluoxetine
Simvastatin	*	*	*	NC	*		5–40	
Spironolactone			I		NC		50–100	Dosage reduction in significant renal impairment
Sulindac	No data	NC	NC	NC	NC		400	Hepatic metabolism to active metabolite; high risk for GI bleed or CNS effects
Tamoxifen	NC	D	*				20–40	Hot flashes, nausea, vomiting
Telithromycin							800	Dosage reduction in significant renal impairment and concomitant hepatic impairment
Telmisartan							40–80	See eprosartan
Temazepam	NC	NC	NC	I	NC	**	15–30	
Terazosin		D	D				1–10	Dose depends on indication; dry mouth and urinary incontinence are common
Tetracycline		I					500–2000	Rarely drug of choice
Theophylline	D	D	I	I		**	0.2–0.4 mg/kg/hr	Elderly more susceptible to side effects: CHF or liver disease decreases clearance: dose based on serum concentrations (7.5–15 mg/L)
Thioridazine		I	NC				10–400	Elderly more susceptible to side effects: prolonged half-life
Ticlopidine	I	D	I				500	Differences among brands; risk of neutropenia; only use in documented allergy to aspirin
Tigecycline							100	No significant PK differences in healthy older adults

Table 5-6. (Continued)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%f)	Time to Peak	Dynamics	Dose (mg/day)	Comment
Timolol							20–80	
Tobramycin	NC	D	I				***	Dose conservatively based on weight and CrCl
Tolazamide							100–1000	
Tolbutamide	D	D	I	I			500–3000	Inactive metabolite excreted via urine
Tolmetin	NC	NC	NC	NC	NC		1200	
Tolterodine	NC	D	I	NC	NC		2–4	Lower doses improve tolerability
Topiramate							50-400	Dose conservatively based on CrCl; initial dose of 25 mg daily and titrate at 25 mg daily at weekly intervals
Toremifene	I		I				60	No dosage reduction required
Tramadol		D	I	NC	NC		200–300	Max dose of 100 mg daily in CrCl < 30 ml/min
Trandolapril	I				I		0.5–4.0	Initiate at lowest dose; use lowest doses in CrCl < 30 ml/min
Trazodone			I		D		50–400	Prolonged half-life; evaluation of therapeutic effect to be delayed
Triamterene		D	I	D			50–100	More effective in combination with thiazide diuretic; avoid in patients with CrCl < 30 ml/min
Triazolam		D	I	I*	I		0.125–0.25	
Trimethoprim-sulfamethoxazole								Dosage reduction based on degree of renal impairment, severity of infection, and susceptibility of causative organisms
							CrCl (ml/min)	Dose
							15–30	One-half usual adult daily dose
							<15	Conflicting data (recommend reduced dose or no use at all)
Trospium	NC	I					20–40	Base dose on tolerability. Increased incidence of anticholinergic side effects in > 75 years of age
Valsartan							80–320	See eprosartan

Valproic acid						Individualize	When used for treatment of agitation associated with dementia, note: serum concentrations do not correlate with behavior response
Venlafaxine		D	I			50–225	Decrease dose by 25% in CrCl 10–70 ml/min. Decrease dose by 50% in hepatic impairment. Minimal side effects make this a valuable alternative in elderly
Verapamil	I	D	I		**	120–480	See amlodipine
Vinblastine	I with chronic doses	NC					
Vincristine	NC	NC					
Warfarin	I	D	I	I*	**	***	Increased age and female sex may increase risk of bleeding; 40% dosage reduction
Ziprasidone						40–200	Does not require dosage modification in the elderly. No additional benefit noted from doses above 20 mg twice daily

[a]PB (%f) = protein binding alterations (percent free fraction); dynamics = pharmacodynamics; dose = recommended daily dosage for geriatric patients; O = oral; P = parenteral; D = decreased; I = increased; NC = no change; * = conflicting data reported; ** = age-related alterations in sensitivity reported; and *** = dose to be individualized for particular patients.

References

1. El Desoky ES. Pharmacokinetic-pharmacodynamic crisis in the elderly. *Am J Ther*. 2007;14:488-98.
2. Klotz U. Pharmacokinetics and drug metabolism in the elderly. *Drug Metab Rev*. 2009;41(2):67-76.
3. Murray MD, Callahan JL. Improving medication use for older adults: an integrated research agenda. *Ann Intern Med*. 2003;139:425-9.
4. Hutchison LC, O'Brien CE. Changes in pharmacokinetics and pharmacodynamics in the elderly patient. *J Pharm Prac*. 2007;20(1):4-12.
5. Greenblatt JD, Harmatz JS, Shader RI. Clinical pharmacokinetics of anxiolytics and hypnotics in the elderly. Part 1. Therapeutic considerations. *Clin Pharmacokinet*. 1991;21(3):165-177.
6. Kane RL, Ouslander JG, Abrass IB, eds. Drug therapy (Chapter 14). In: *Essentials of Clinical Geriatrics*. New York: McGraw-Hill; 2004:357-88.
7. Ahmed N, Mandel R, Fain MJ. Frailty: an emerging geriatric syndrome. *Am J Med*. 2007;120:748-53.
8. Wynne HT, Cope LH, James OFW, et al. The effect of age and frailty upon acetanilide clearance in man. *Age Ageing*. 1989;18:415-6.
9. Fried PL. The epidemiology of frailty: The scope of the problem. In: Perry HM, Morley JE, Coe RM, eds. *Aging, Musculoskeletal Disorders and Care of the Frail Elderly*. New York, NY: Springer; 1993:3-16.
10. Hubbard RE, O'Mahoney MS, Calver BI, et al. Plasma esterases and inflammation in ageing and frailty. *Eur J Clin Pharmacol*. 2008;64(9):895-900.
11. Noreddin AM, Haynes V. Use of pharmacodynamic principles to optimize dosage regimens for antibacterial agents in the elderly. *Drugs Aging*. 2007;24(4):275-92.
12. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharm*. 2003;57(1):6-14.
13. Muhlberg W. Pharmacokinetics of diuretics in geriatric patients. *Arch Gerontol Geriatr*. 1989;9(3):283-6.
14. Abernathy DR, Schwartz JB, Todd ED, et al. Verapamil pharmacodynamics and disposition in young and elderly hypertensive patients: Altered electrocardiographic and hypotensive responses. *Ann Intern Med*. 1986;105(3):329-36.
15. Montamat SC, Abernathy DR. Calcium antagonists in geriatric patients: Diltiazem in elderly persons with hypertension. *Clin Pharmacol Ther*. 1989;45:682-5.
16. Robertson DRC, Waller DG, Renwick AG, et al. Age-related changes in the pharmacokinetics and pharmacodynamics of nifedipine. *Br J Clin Pharmacol*. 1988;25(3):297-305.
17. Piepho RW, Fendler KJ. Antihypertensive therapy in the aged patient: Clinical pharmacokinetic considerations. *Drugs Aging*. 1991;1:94.
18. Rocci ML, Vlasses PH, Cressman MD, et al. Pharmacokinetics and pharmacodynamics of labetalol in elderly and young hypertensive patients following single and multiple doses. *Pharmacotherapy*. 1990;10(2):92-9.
19. Creasey WA, Funke PT, McKinstry DN, et al. Pharmacokinetics of captopril in elderly healthy male volunteers. *J Clin Pharmacol*. 1986;26(4):264-8.
20. Kobayashi KA, Bauer LA, Horn JR, et al. Glipizide pharmacokinetics in young and elderly volunteers. *Clin Pharm*. 1988;7(3):224-8.
21. Schwinghammer TL, Antal EJ, Kubacka RT, et al. Pharmacokinetics and pharmacodynamics of glyburide in young and elderly nondiabetic adults. *Clin Pharm*. 1991;10(7):532-8.
22. Greenblatt JD, Harmatz JS, Shader RI. Clinical pharmacokinetics of anxiolytics and hypnotics in the elderly. Part 2. Therapeutic considerations. *Clin Pharmacokinet*. 1991;21(4):262-73.
23. LeBel M, Barbeau G, Bergeron MG, et al. Pharmacokinetics of ciprofloxacin in elderly subjects. *Pharmacotherapy*. 1986;6(2):87-91.
24. Divoll M, Abernathy DR. Acetaminophen kinetics in the elderly. *Clin Pharmacol Ther*. 1981;31(2):151-6.
25. Johansson LC, Frison L, Logren U, et al. Influence of age on the pharmacokinetics and pharmacodynamics of Ximelagatran, an oral direct thrombin inhibitor. *Clin Pharmacokinet*. 2003;42(4):381-92.
26. Guay DRP. Clinical pharmacokinetics of drugs used to treat urge incontinence. *Clin Pharmacokinet*. 2003;42(14):1243-85.
27. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives zaleplon, zolpidem, and zopiclone. *Clin Pharmacokinet*. 2004;43(4): 227-38.
28. Aronow WS, Frishman WH, Cheng-Lai A. Cardiovascular drug therapy in the elderly. *Cardiology Rev*. 2007;15(4):195-215.
29. Beyth RJ, Shorr RI. Principles of drug therapy in older patients: rational drug prescribing. *Clin Geriatr Med*. 2002;18:577-692.

30. Grandison MK, Boudinot FD. Age-related changes in protein binding of drugs: Implications for therapy. *Clin Pharmacokinet.* 2000;38:271-90.
31. Grond S, Radbruch L, Lehmann KA. Clinical pharmacokinetics of transdermal opioids. *Clin Pharmacokinet.* 2000;38(1):59-89.
32. Owen JA, Sitar DS, Berger L, et al. Age-related morphine kinetics. *Clin Pharmacol Ther.* 1983;34:364-8.
33. Hasselgren G, Hassan-Alin M, Andersson T, et al. Pharmacokinetic study of esomeprazole in the elderly. *Clin Pharmacokinet.* 2001;40(2):145-50.
34. Hatanaka T. Clinical pharmacokinetics of pravastatin, mechanisms of pharmacokinetic events. *Clin Pharmacokinet.* 2000;39(6):397-412.
35. Scripture CD, Peiper JA. Clinical pharmacokinetics of fluvastatin. *Clin Pharmacokinet.* 2001;40(4):263-81.
36. Song JC, White CM. Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors, an update. *Clin Pharmacokinet.* 2002;41(3);207-24.
37. Kelly JG, O'Malley K. Clinical pharmacokinetics of the newer ACE inhibitors. A review. *Clin Pharmacokinet.* 1990;19:375-84.
38. Morello KC, Wurz GT, DeGregorio MW. Pharmacokinetics of selective estrogen receptor modulators. *Clin Pharmacokinet.* 2003;42(4):361-72.
39. Oberbauer R, Kivanek P, Turnheim K. Pharmacokinetics of indomethacin in the elderly. *Clin Pharmacokinet.* 1993;24:428-34.
40. DeVane CL, Liston HL, Markowitz JS. Clinical pharmacokinetics of sertraline. *Clin Pharmacokinet.* 2002;41(15):1247-66.
41. Fischer JH, Patel TV, Fischer PA. Fosphenytoin, clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. *Clin Pharmacokinet.* 2003;42(1):33-58.
42. Lenz TL, Wilson AF. Clinical pharmacokinetics of antiplatelet agents used in the secondary prevention of stroke. *Clin Pharmacokinet.* 2003;42(10):909-20.
43. Kaye CM, Nicholls B. Clinical pharmacokinetics of ropinirole. *Clin Pharmacokinet.* 2000;39(4):243-54.
44. Aminimanizani A, Beringer P, Jelliffe R. Comparative pharmacokinetics and pharmacodynamics of the newer fluoroquinolone antibacterials. *Clin Pharmacokinet.* 2001;40(3):169-87.
45. Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age. *Clin Pharmacokinet.* 2006;45(4):351-63.
46. Jann MW, Shirley KL, Small GW. Clinical pharmacokinetics and pharmacodynamics of cholinesterase inhibitors. *Clin Pharmacokinet.* 2002;41(10):719-39.
47. Harper CM, Newton PA, Walsh JR. Drug-induced illness in the elderly. *Postgrad Med.* 1989;86(2):245-56.
48. Kusserow R. Drug misuse among the older patients. Report of the Inspector General of the U.S. Department of HHS, January 1989.
49. Colt HG, Shapiro AP. Drug-induced illness as a cause for admission to a community hospital. *J Am Geriatr Soc.* 1989;37:323.
50. Geurian KL, Pitner RB, Lackland DT. Potential drug-drug interactions in an ambulatory geriatric population. *J Geriatr Drug Ther.* 1992;7(2):67-86.
51. Schneider JK. Adverse drug reactions in an elderly outpatient population. *Am J Hosp Pharm.* 1992;49:90.
52. Gurwitz JH, Avorn J. The ambiguous relation between aging and adverse drug reactions. *Ann Intern Med.* 1991;114(11):957-66.
53. Beyth RJ, Shorr RI. Epidemiology of adverse drug reactions in the elderly by drug class. *Drugs Aging.* 1999;14(3):231.
54. Budnita DS, Pollock DA, Weidenbach KN, et al. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA.* 2006;296(15):1858-66.
55. Klein LE, German PS, Levine DM. Adverse drug reactions among the elderly: a reassessment. *J Am Geriatr Soc.* 1981;29:525-30.
56. Nolan L, O'Malley K. Prescribing for the elderly. Part I: sensitivity of the elderly to adverse drug reactions. *J Am Geriatr Soc.* 1988;36:142-9.
57. Terrell KM, Heard K, Miller DK. Prescribing to older ED patients. *Am J Emerg Med.* 2006;24:468-78.
58. Chutka DS, Takahashi PY, Hoel RW. Inappropriate medications for elderly patients. *Mayo Clin Proc.* 2004;79:122-39.
59. Col N, Fangle JE, Kronholm P. The role of medication noncompliance and adverse drug reaction in hospitalization of the elderly. *Arch Intern Med.* 1990;150(4):841-5.
60. Resnick NM, Marcantonio DR. How should clinical care of the aged differ? *Lancet.* 1997;350:1157-8.

61. Hammerlein A, Derendorf H, Lowenthal DT. Pharmacokinetic and pharmacodynamic changes in the elderly: clinical implications. *Clin Pharmacokinet.* 1998;35(1):49-64.
62. Dawling S, Crome P. Clinical pharmacokinetic considerations in the elderly: an update. *Clin Pharmacokinet.* 1981;17:236-63.
63. Hilmer SN, McLachlan, Le Couteur DG. Clinical pharmacology in the geriatric patient. *Fundam Clin Pharmacol.* 2007;21:217-30.
64. Cahpron DJ. Drug disposition and response. In: Delafuente JC, Stewart RB, eds. *Therapeutics in the Elderly.* Cincinnati, OH: Harvey Whitney Books; 2001:257-88.
65. Evans MA, Triggs EJ, Broe GA, et al. Systemic availability of orally administered L-dopa in the elderly Parkinsonian patient. *Eur J Clin Pharmacol.* 1980;17:215-21.
66. Bianchine JR, Calimlim LR, Morgan JP, et al. Metabolism and absorption of L-3,4 dihydroxyphenylalanine in patients with Parkinson's disease. *Ann NY Acad Sci.* 1971;179:126-40.
67. Ochs HR, Greenblatt DJ, Allen MD, et al. Effect of age and Billroth gastrectomy on absorption of desmethyldiazepam from chlorazepate. *Clin Pharmacol Ther.* 1979;26:449-56.
68. Lamy PP. *Prescribing for the Elderly.* Littleton, MA: PSG Wright;1980.
69. Kelly JG, McGarry K, O'Malley K, et al. Bioavailability of labetalol increases with age. *Br J Clin Pharmacol.* 1982;14:304-5.
70. Storstein L, Larsen A, Saevareld L. Pharmacokinetics of calcium channel blockers in patients with renal insufficiency and in geriatric patients. *Acta Med Scand.* 1984;681:25-30.
71. Ewy GA. Digoxin metabolism in the elderly. *Circulation.* 1969;39(4):449-52.
72. Rubin PC, Scott PJW, Reid JL. Prazosin disposition in young and elderly subjects. *Br J Clin Pharmacol.* 1981;12(3):401-4.
73. Cusack BJ. Pharmacokinetics in older persons. *Am J Geriatr Pharmcother.* 2004;2:274-302.
74. Miller SW, Strom JG. Drug-product selection: implications for the geriatric patient. *The Consult Pharm.* 1990;5(1):30-7.
75. Greenblatt DJ. Reduced serum albumin concentration in the elderly: a report from the Boston Collaborative Drug Surveillance Program. *J Am Geriatr Soc.* 1979;27:20-2.
76. Cooper JW, Cobb HH. Nutritional correlation and changes in a geriatric nursing home. *Nut Supp Serv.* 1988;8(8):5-7.
77. Michalets EL. Update: Clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy.* 1998;18(1):84-112.
78. Schmucker DL. Aging and drug disposition: an update. *Pharmacol Rev.* 1985;37:133-48.
79. Wallace SM, Verbeek RO. Plasma protein binding of drugs in the elderly. *Clin Pharmacokinet.* 1987;12(1):41-72.
80. Somerville K, Faulkner G, Langman M. Non-steroidal anti-inflammatory drugs and bleeding peptic ulcer. *Lancet.* 1986;1:462-4.
81. Hayes MJ, Langman MJS, Short AH. Changes in drug metabolism with increasing age. *Br J Clin Pharmacol.* 1975;12(2):73-79.
82. Mather LE, Tucker GT, Pflug AE. Meperidine kinetics in man. *Clin Pharmacol Ther.* 1975;17(1):21-30.
83. Beers MH, Ouslander JG, Fingold SF, et al. Inappropriate medication prescribing in skilled-nursing facilities. *Ann Intern Med.* 1992;117:684-9.
84. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly, an update. *Arch Intern Med.* 1997;157:1531-6.
85. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults. *Arch Intern Med.* 2003;163:2716-24.
86. Greenblatt DJ, Sellers EM, Shader RI. Drug disposition in old age. *N Engl J Med.* 1982;306(18):1081-8.
87. Chapron DI. Drug disposition and response. In: Delafuente JC, Stewart RB, eds. *Therapeutics in the Elderly.* 3rd ed. Cincinnati, OH: Harvey Whitney Books Company, 2001:257-88.
88. Dawling S, Lynn K, Rosser R, et al. Nortriptyline metabolism in chronic renal failure: metabolic elimination. *Clin Pharmacol Ther.* 1982;32(3):322-9.
89. Abernathy DR, Greenblatt DJ, Shader RI. Imipramine and desipramine disposition in the elderly. *J Pharmacol Exp Ther.* 1985;232:183-8.
90. Cohen BM, Sommer BR. Metabolism of thioridazine in the elderly. *J Clin Psychopharmacol.* 1988;8(5):336-9.
91. Antal EJ, Kramer PA, Mercik SA. Theophylline pharmacokinetics in advanced age. *Br J Clin Pharmacol.* 1981;12(5):637-5.
92. Kinirons MT, O'Mahoney M. Drug metabolism and ageing. *Br J Clin Pharmacol.* 2004;57:540-4.
93. Kinirons MT, Crome P. Clinical pharmacokinetic consideration in the elderly, an update. *Clin Pharmacokinet.* 1999;33:302-12.
94. LeBlanc JM, Dasta JF, Pruchnicki MC, et al. Impact of disease states on the pharmacokinetics and pharmacodynamics of angiotensin-converting enzyme inhibitors. *J Clin Pharmacol.* 2006;46:968-80.

95. Gral T, Young M. Measured versus estimated creatinine clearance in the elderly as an index of renal function. *J Am Geriatr Soc*. 1980;28(11):492-6.

96. Smythe M, Hoffman J, Kizy K, et al. Estimating creatinine clearance in elderly patients with low serum creatinine concentrations. *Am J Hosp Pharm*. 1994;51(2):198-204.

97. Smith JM, Baldessarini RJ. Changes in prevalence, severity, and recovery in tardive dyskinesia with age. *Arch Gen Psych*. 1980;37:1368-73.

98. Feely J, Cloakley D. Altered pharmacodynamics in the elderly. *Clin Geriatr Med*. 1990;6:269-83.

99. Uchida H, Mamo DC, Mulsant BH, et al. Increased antipsychotic sensitivity in elderly patients: evidence and mechanisms. *J Clin Psych*. 2009;70(3):397-405.

100. Committee on Identifying and Preventing Medication Errors, Aspden P, Wolcott J, Bootman JL, et al., eds. *Preventing Medication Errors. Quality Chasm Series Institute of Medicine Report*. Institute of Medicine of the National Sciences; July, 2006. Available at: http://www.iom/CMS/3809/22526/35939.aspx. Accessed 12/01/06.

101. Sloane PD, Zimmerman S, Brown LC, et al. Inappropriate medication prescribing in residential care/assisted living facilities. *J Am Ger Soc*. 2002;50:1001-11.

102. Spore DL, Mor V, Larrat P, et al. Inappropriate drug prescriptions for elderly residents of board and care facilities. *Am J Public Health*. 1997;87:404-9.

103. Golden AG, Preston RA, Barnett SD, et al. Inappropriate medication prescribing in homebound older adults. *J Am Ger Soc*. 1999;47:948-53.

104. Hanlon JT, Fillenbaum GG, Schmader KE, et al. Inappropriate drug use among community dwelling elderly. *Pharmacother*apy. 2000;20:575-82.

105. Goulding MR. Inappropriate medication prescribing for elderly ambulatory patients. *Arch Intern Med*. 2004;164:305-12.

106. Aparasu RR, Fliginger SE. Inappropriate medication prescribing for the elderly by office-based physicians. *Ann Pharmacother*. 1997;31:823-9.

107. Huang B, Bachmann KA, He X, et al. Inappropriate prescriptions for the aging population of the United States: an analysis of the National Ambulatory Medical Care Survey, 1997. *Pharmacoepidemiol Drug Saf*. 2002;11:127-34.

108. Caterino JM, Emond JA, Camargo Jr CA. Inappropriate medication administration to the acutely ill elderly: a nationwide emergency department study, 1999–2000. *J Am Ger Soc*. 2004;52:1847-55.

109. Bonk ME, Krown H, Matuszewski K, et al. Potentially inappropriate medications in hospitalized senior patients. *Am J Hosp Pharm*. 2006;63:1161-65.

110. Stefanacci RG, Cavallaro E, Beers MH, et al. Developing explicit positive Beers criteria for preferred central nervous system medications in older adults. *Cons Pharm*. 2009;24(8):601-10.

111. Semla TP, Beizer JL, Higbee MD, eds. *Geriatric Dosage Handbook*. 15th ed. Hudson, OH: Lexi-Comp; 2010.

112. Aronoff GR, Bennett WM, Berns JS, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*. 5th ed. Philadelphia, PA: ACP-ASIM; 2007.