Pharmacokinetic and Pharmacodynamic Alterations in the Geriatric Patient

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With publication of this article, The Consultant Pharmacist *begins a series called* Geriatric Primer. *These articles will address key issues related to the proper use of medications in the elderly. Why a geriatric primer? As consultant pharmacists are well aware, managing the use of medications in the elderly is a complex process. The elderly are the highest consumers of medications and have a greater burden of medical conditions.*

Despite these compelling facts, the unique needs of the elderly frequently are not given adequate attention during pharmacy education and training. In light of this, the series is targeted at several audiences: the new pharmacy practitioner, those with experience in other practice settings who want to enhance their knowledge about medication use in the elderly, and experienced practitioners who would like a review of key subject areas. The authors of these articles were carefully selected based on extensive knowledge in the subject areas and experience in serving as a senior care pharmacy provider.

We hope that these articles will be helpful to all those who seek to provide excellent care to seniors in all settings.

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Adverse drug events (ADEs) are all too common in older patients. Although there are multiple causes for the ADEs in the elderly, alterations in pharmacokinetics (PK) and pharmacodynamics (PD) are frequent culprits. These alterations in PK and PD may be part of the normal aging process. Older patients often develop significant drug-related problems when alterations in PK and PD are not appropriately accounted for in prescribing and monitoring of medications. Clinically, the most significant PK changes that occur in aging are renal elimination and metabolism of drugs. In general, renal function declines with aging, necessitating dosage adjustments for drugs with renal-elimination pathways. The ability of the liver to metabolize certain drugs may also decline as a consequence of the aging process. From a PD standpoint, exaggerated responses are frequent, and often it is the side effects of medications that become exaggerated, rather than the therapeutic effects. Drugs affecting the central nervous system are particularly prone to PD alterations. Because of the PK and PD changes, vigilant monitoring of both therapeutic and adverse effects is mandatory in older patients. Based on PK and PD differences between middle-aged and elderly patients, there are certain medications that should almost always be avoided in older people. In addition, because older people tend to use more medications, the incidence of drug-drug interactions becomes more prevalent. Most of the drug-drug interactions that adversely impact older people involve both PK and PD mechanisms. Pharmacists and all prescribers must have a sound understanding of PK and PD effects of medications used in older people to provide optimal care and avoid preventable drug-related problems.

Key words: Adverse drug events, Aging, Pharmacodynamics, Pharmacokinetics.

Abbreviations: ADE = Adverse drug events, CrCl = Creatinine clearance, CYP = Cytochrome P 450, IBW = Ideal body weight, NSAID = Nonsteroidal anti-inflammatory drug, PD = Pharmacodynamics, PK = Pharmacokinetics.

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Introduction

The geriatric population, usually defined as age 65 years and older, is growing rapidly. The first of the baby boomers turn 65 years old in 2011. The geriatric population made up 12.4% of the total U.S. population in 2000, and by 2020 the geriatric population will grow to more than 16% of the population.[1] The impact of the baby boomers is emphasized by the fact that in 1988 there were 30 million people aged 65 years and older. Twenty-three years later, in 2011, this number will be 40 million; however, this number will increase by another 10 million in only eight years (2019). Perhaps more important is that the very elderly cohort, those age 85 years and older, are the fastest growing segment among seniors. This is extremely important to health care because these individuals utilize a disproportionate amount of health care services, including medications. Overall, geriatric patients use about 40% of acute hospital bed days, use more than 30% of all prescription medications, and consume more than 40% of nonprescription medications.[2] Trends over recent years show that medication use has been increasing among the elderly. With the enactment of the Medicare Modernization Act of 2003 (Medicare Part D), prescription medications will be more easily available to many seniors who previously have been unable to afford them. In addition, more than 80% of elderly people have at least one chronic disease. As the elderly population continues to grow at unprecedented rates, especially the very old, the amount of chronic illness and medication use is likely to increase at dramatic rates. The cost of health care utilization by the elderly population has tremendous implications for health insurance companies, hospitals and health systems, the health care workforce, governments, individuals in their retirement years—and pharmacists.

Adverse Drug Events

Although medication therapy improves patients' quality of life and can be lifesaving, it can also cause morbidity and mortality. Nearly one-third of hospitalizations of older people are caused by their medications—mostly from adverse side effects or by patients not following the directions appropriately.[3] A well-conducted study in more than 30,000 ambulatory geriatric patients identified an alarming high rate of preventable adverse drug events (ADEs).[4] Of the ADEs that occurred in this population during the 12-month study period, 27.6% were deemed preventable. Preventable in this study was defined as ADEs that were caused by an error and were preventable by any means available. Using structured criteria, an expert panel judged the preventability of the error. Perhaps most important is the fact that 42.2% of preventable ADEs in these elderly patients were considered to be serious, life-threatening, or fatal. Those ADEs that were most serious were also considered to be the most likely events that could have been prevented. Of all the preventable ADEs, almost 59% occurred from prescribing, such as using a medication or dose that is inappropriate for an elderly population, and more than 60% of ADEs occurred because of poor monitoring. (These percentages add up to more than 100% because more than one contributing factor for an ADE occurred in individual patients.) Examples of poor monitoring are failure to obtain a potassium serum concentration in a patient receiving a loop diuretic, failure to monitor for gastrointestinal (GI) bleeding in a patient using nonsteroidal anti-inflammatory drugs (NSAIDs), and failure to make dosage adjustments in warfarin therapy when an international normalized ratio was not in the therapeutic range. Also, poor patient adherence was responsible for more than 20% of ADEs, and insufficient patient education about medications also contributed to a significant proportion of ADEs. Pharmacists, physicians, nurses, and other health care providers clearly have a role to play detecting and correcting many of the causes of preventable ADEs.

Risk factors for ADEs in older patients are identified in Table 1.[5,6] Similar lists of risk factors have been generated from numerous research studies. Identifying risk factors in patients will help health care providers select appropriate patients that could benefit from interventions, and hopefully prevent a serious ADE from occurring.

Older individuals are at increased risk of ADEs from drug therapy, and there are numerous reasons for this phenomenon. Normal physiologic processes that occur as adults age can impact how medications act in the body. Some of the increased risk can be explained by alterations in physiology and disease, which affect pharmacokinetics (PK), and pharmacodynamics (PD). PD deals with how the body handles the medication from the time the medication is administered until it is eliminated from the body. PD refers to how the body

responds to the medication. Both PK and PD alterations occur in older adults and contribute to ADEs in this patient population.

Pharmacokinetic Alterations in Aging

Pharmacokinetic parameters can be divided into four categories based on how the body handles the medication. These categories are absorption, distribution, metabolism, and renal elimination. Each of these parameters can be affected by normal changes in physiology as a result of the aging process or diseases that are common among the elderly population. Each of these pharmacokinetic parameters is discussed below. Although there are numerous studies on pharmacokinetic alterations in aging, most are conducted in healthy elderly subjects. It may not be appropriate to extrapolate these data into sick or frail elderly, as illness may impart changes to PK.

Absorption

Many physiologic changes occur in the stomach and intestinal tract as part of normal aging. In many older people, secretion of hydrochloric acid diminishes. It may take longer for the stomach contents to empty into the small bowel, and transit time through the bowels may be increased.[7] Most orally administered medications are passively absorbed in the small bowel, and aging does not seem to alter drug absorption to a large extent. There are exceptions, particularly for medications requiring active transport mechanisms such as vitamin B_{12}, calcium, and iron that have reduced absorption in the elderly.[7] Diseases such as heart failure may cause decreased blood flow to the intestinal tract and could decrease absorption. Oral furosemide absorption has been shown to be impaired during decompensated heart failure, possibly because of slow gastric emptying, which may contribute to furosemide resistance often seen in worsening heart failure.[8] As a general rule, healthy elderly individuals maintain normal oral drug absorption, but diseases affecting the GI system can impair absorption.

More and more medications are being formulated into topical products such as patches and gels. There is little information available about the effects of aging on this method of drug delivery. Aging skin atrophies and becomes thinner, and transdermal drug absorption may be impaired because of reduced blood flow to the skin. Elevated body temperature has been shown to increase fentanyl absorption from the transdermal patch, requiring cautious use in patients with fever.[9] This phenomenon may apply to other topical products as well. Intramuscular and subcutaneous injections also may have altered pharmacokinetics in older people. Muscle mass may be significantly decreased in older patients, particularly the frail elderly. As with other sites of absorption, there may be poor blood perfusion to the muscle or subcutaneous tissues from cardiovascular disease that can impair drug absorption. In such circumstances other routes of administration may need to be selected.

Table 1. Selected Risk Factors for Adverse Drug Events in the Elderly

Age ≥ 85 years
Depression
Female gender
Low body weight or BMI < 22 kg/m^2
Use of 5 or more medications
Use of multiple pharmacies
Dementia
Renal impairment

Abbreviation: BMI = Body mass index.
Source: Reference 5.

Distribution

Once a medication has been absorbed from its site of administration, it enters the circulation and gets distributed throughout the body. The nature of the drug molecule will influence if it gets distributed mostly to the water compartment (plasma), lean muscle tissue, or to body fat. The term volume-of-distribution is commonly used to describe the extent of drug distribution to tissues, relative to the plasma volume. Aging is associated with a decrease in the amount of total body water. Therefore, water-soluble medications such as digoxin, ethanol, lithium, theophylline, and morphine will have a decreased volume of distribution, making their serum concentrations higher in an elderly person if given the same dose as a middle-aged adult. Under these circumstances smaller doses would be needed to avoid potential toxicity. Since muscle mass tends to decrease

with age, the volume of distribution for medications that distribute to lean tissue is smaller; digoxin is an example of such a medication. Again, lower doses are mandated to prevent toxicity. The percentage of body fat tends to increase in the geriatric population. This may be more related to lifestyle changes than to normal aging processes. Nonetheless, in general, lipid-soluble medications will have a larger volume of distribution in aged patients. Examples of lipid-soluble medications are phenytoin, valproic acid, diazepam, lidocaine, and oxazepam. Because of the larger volume of distribution, lipid-soluble medications tend to stay in the body longer, potentially prolonging their duration of action. In such circumstances, drug dosing needs to be reduced or the intervals between dosing administration should be increased to avoid adverse effects.

Many medications bind to serum proteins, mostly albumin or alpha$_1$-acid glycoprotein. Aging does not significantly affect either of these two proteins; however, malnourished or frail elderly may have markedly decreased serum albumin concentrations. A medication that is highly bound to albumin in a patient with a very low albumin level will result in more of the unbound drug in the circulation. It is the unbound drug that is pharmacologically active. In such circumstances patients may become toxic from an increase in the unbound portion of the drug, even if the total drug concentration (bound and unbound) is within the therapeutic range. This is particularly true for medications with a narrow therapeutic index where there is a fine line between therapeutic levels and toxic levels. Phenytoin is a good example of a highly protein-bound medication. During states of hypoalbuminemia, the unbound fraction of phenytoin can double.[10] During prolonged illness, albumin concentrations can decrease, warranting phenytoin dosage adjustments. Alpha$_1$-acid glycoprotein is an acute-phase reactant and significantly increases during illness. Alpha$_1$-acid glycoprotein tends to remain normal or increase slightly with age, and its clinical importance, as a consequence of aging, has not been fully clarified.

Metabolism

The liver serves as a major site for drug metabolism. It metabolizes medications to active and inactive compounds through oxidation, reduction, or hydrolysis (Phase I reactions). For some medications, known as prodrugs, an inactive drug is administered and becomes activated after liver metabolism occurs. The liver conjugates some medications to large molecules to make them more water soluble and more easily eliminated through the kidneys or biliary tract (Phase II reactions). Phase I liver metabolism of medications is often reduced in older patients. The precise reasons for this phenomenon have not been unequivocally determined. Normal aging physiology causes the liver to become smaller, and liver blood perfusion diminishes. The data on the effect of liver metabolism are not straightforward; some studies show an age-related decline in metabolism, while other studies do not. This can be explained, in part, by two factors: a relatively few number of individuals usually are used in metabolism studies and individuals have large variabilities in metabolism.

The cytochrome P450 (CYP) system is responsible for the metabolism (Phase I reactions) of many medications. There are six major CYP isoenzymes that are responsible for drug metabolism: CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. More than 50% of currently used medications that are metabolized undergo CYP3A4 metabolism.[11] Present thinking is that aging decreases metabolism of medications through the CYP1A2 and CYP2C19 pathways, decreases or remains normal for medications undergoing metabolism via CYP3A4 and CYP2C9, and is unchanged for medications metabolized by CYP2D6.[12] A good rule of thumb is to start with the lowest effective dose, when possible, for any medication used in older patients that undergoes CYP metabolic pathways. This way, if metabolism is decreased in an individual patient, toxicity from altered metabolism is less likely to occur.

Not all medications that are metabolized in the liver undergo CYP metabolism. Some medications go through conjugation pathways (Phase II reactions) such as acetylation, glucuronidation, or sulfation for elimination. Aging does not alter these processes.

As mentioned earlier, frailty may alter metabolism. Keep in mind that most studies are conducted in healthy elderly people. Even though current thinking is that the aging process spares some metabolic pathways, in frail elders it is best to err on the safe side and assume metabolism may be decreased. This will require starting with low doses of medication.

Table 2 lists selected medications commonly used in

Table 2. Selected Medications and the Cytochrome P450 System

CYP1A2

Substrates	Inhibitors	Inducers
Acetaminophen	Amiodarone	Carbamazepine
Amitriptyline	Ciprofloxacin	Phenobarbital
Caffeine	Citalopram	Phenytoin
Clopidogrel	Diltiazem	Smoking
Diazepam	Erythromycin	
Haloperidol	Levofloxacin	
Mirtazapine	Omeprazole	
Olanzapine	Paroxetine	
Propranolol		
Verapamil		

CYP2C9

Substrates	Inhibitors	Inducers
Amitriptyline	Amiodarone	Carbamazepine
Celecoxib	Clopidogrel	Phenobarbital
Diazepam	Fluoxetine	Phenytoin
Dronabinol	Lovastatin	
Fluoxetine	Metronidazole	
Glimepiride	Paroxetine	
Glipizide	Sulfonamides	
Losartan		
Omeprazole		
Phenytoin		
Quetiapine		
Sildenafil		
Valsartan		

CYP2C19

Substrates	Inhibitors	Inducers
Amitriptyline	Citalopram	Carbamazepine
Cilostazol	Felbamate	Phenobarbital
Citalopram	Fluoxetine	Phenytoin
Diazepam	Lansoprazole	Prednisone
Imipramine	Omeprazole	
Lansoprazole	Sertraline	
Phenytoin	Topiramate	
Quetiapine		
Rabeprazole		
Topiramate		

CYP2D6

Substrates	Inhibitors	Inducers
Amitriptyline	Celecoxib	Carbamazepine
Carvedilol	Chlorpheniramine	Ethanol
Codeine	Citalopram	Phenobarbital
Donepezil	Fluoxetine	Primidone
Fentanyl	Haloperidol	
Fluoxetine	Paroxetine	
Haloperidol	Propoxyphene	
Hydrocodone		
Meperidine		
Metoprolol		
Morphine		
Olanzapine		
Oxycodone		
Quetiapine		
Risperidone		
Timolol		
Tolterodine		
Trazodone		

CYP3A4

Substrates	Inhibitors	Inducers
Alprazolam	Amiodarone	Carbamazepine
Amlodipine	Ciprofloxacin	Phenobarbital
Astemizole	Clarithromycin	Phenytoin
Atorvastatin	Diltiazem	Primidone
Buspirone	Erythromycin	
Carbamazepine	Fluoxetine	
Citalopram	Grapefruit juice	
Clarithromycin	Itraconazole	
Diazepam	Ketoconazole	
Diltiazem	Metronidazole	
Donepezil	Sertraline	
Erythromycin	Verapamil	
Felodipine		
Finasteride		
Haloperidol		
Ketoconazole		
Losartan		
Nifedipine		
Quetiapine		
Sildenafil		
Simvastatin		
Trazodone		
Verapamil		

elderly people and the medications' major metabolic pathway. Some medications have more than one CYP pathway for metabolism. Medications can also induce CYP enzymes, resulting in increased drug metabolism. Likewise, some medications can inhibit CYP enzymes, resulting in decreased drug metabolism. Medications inducing or inhibiting metabolism and medications competing for the same enzymatic pathway are the basis for many clinically significant drug-drug interactions. Prescribers and pharmacists must be aware of the metabolic pathways involved with all medications that a patient may be taking to minimize ADEs.

Renal Elimination

Elimination of medications via the kidney decreases with advancing age. Cross-sectional and longitudinal studies indicate that renal functions decline with increasing age; the number of functioning glomeruli decreases, renal blood flow decreases, and tubular functions decline. Glomerular filtration declines by 25% to 50% between 20 and 90 years of age.[13] Although not all elderly will have significantly impaired renal function, it is prudent to assume that for renally eliminated medications a lower dose should be used in elderly patients.

Many medications are dosed based on serum creatinine or creatinine clearance (CrCl). CrCl is used to approximate the glomerular filtration rate. The most accurate method to determine CrCl is to measure it, but this requires collecting all urine for 24 hours, a very cumbersome task. There are numerous methods for estimating CrCl, but the most commonly used is the Cockcroft-Gault equation. This equation uses the patient's serum creatinine concentration, age, and weight:

$CrCl_{male}$ = [(140-age)(IBW)]/[72(serum creatinine)], where age is in years, ideal body weight (IBW) is in kg, and serum creatinine is in mg/dL. For women, the result is multiplied by 0.85. Renal function must be stable for this formula to be useful. In people weighing less than their ideal body weight, their actual weight in kg is used in the Cockcroft-Gault equation. In frail patients, whose muscle mass is markedly diminished, using the Cockcroft-Gault equation will overestimate renal function. This is because creatinine is derived from muscle, and patients with little muscle mass produce low amounts of creatinine. For elderly patients, some clinicians will round up the serum creatinine to 1.0 when the serum concentration is less than 1.0, but there are no convincing studies to suggest this procedure is valid. Calculating a CrCl is only an estimate to assist in determining a dose of a renally eliminated medication. Serum drug concentrations should be measured for medications with narrow therapeutic indices to ensure accurate dosing, and close monitoring for adverse effects is imperative. Commonly used medications in the elderly that are renally eliminated are shown in Table 3.

Pharmacodynamics

Normal and disease-associated physiologic changes in aging can greatly affect the body's response to drug therapy. These changes in PD can enhance or impede drug actions, depending on the medication. While pharmacokinetic alterations in aging are well studied, there are many fewer data in age-related pharmacodynamic changes. Altered PD may be the result of changes in receptor affinity for medication, postreceptor events such as signals from the cell membrane receptor to the cell nucleus, or from altered homeostatic control mechanisms.[14,15] No generalization about altered PD can be made because both increases and decreases in drug action have been reported for many medications, and other medications produce no changes.

In aging populations, a single medication with multiple pharmacodynamic actions can have some actions blunted and other actions exacerbated. Verapamil is an example of such a medication. In a small study, verapamil was administered to a group of young adults (mean age = 29 years), a group of elderly (mean age = 68 years), and a group of very elderly (mean age = 84 years), and various pharmacodynamic parameters were assessed.[16] The elderly subjects had less prolongation in the P-R interval on the electrocardiogram, compared with the young subjects. In older people, higher serum concentrations of verapamil were needed to achieve the same level of P-R prolongation as young adults. Increased heart rate was seen in the young group, and decreases in heart rate occurred in the elderly groups. The increased heart rate in the young is most likely the result of a reflex tachycardia induced by vasodilation from the medication. Older people are known to have baroreflex responses that are blunted, which probably explains the lack of heart rate increase. Verapamil also had more blood pressure (BP) lowering in the elderly groups compared with the young

Table 3. Commonly Used Medications That Are Eliminated Renally

Acebutolol	Glyburide*
Allopurinol	Lisinopril
Amantadine	Lithium
Amiloride	Metformin
Aminoglycosides	Methotrexate
Atenolol	Nadolol
Baclofen	Norfloxacin
Benazepril	Ofloxacin
Captopril	Pindolol
Ciprofloxacin	Procainamide
Clonidine	Quinipril*
Digoxin	Ramipril*
Diltiazem*	Ranitidine
Enalapril	Risperidone*
Famotidine	Tetracycline
Fosinopril	Vancomycin
Gabapentin	

*Has an active major metabolite that is renally eliminated.

group, suggesting that the elderly are more sensitive to the vasodilator effects of verapamil.

Another example of altered PD is seen with benzodiazepines. Midazolam is a short-acting benzodiazepine frequently used during diagnostic or surgical procedures. Two groups of patients, young and old, received intravenous midazolam prior to a dental procedure, and pharmacokinetic and pharmacodynamic measures were obtained.[17] Despite using a lower dose in the elderly group, reaction time was more blunted in the seniors, and their rating of sedation was higher than the younger group. Even when the results were normalized for differences in pharmacokinetic parameters, the data clearly showed that the elderly patients were more sensitive to the central nervous system (CNS) effects of midazolam. This phenomenon can be extrapolated to most medications that affect the CNS. Elderly patients frequently show increased sensitivity to CNS agents, such as benzodiazepines, antipsychotic agents, and narcotic analgesics, and this increased sensitivity is often the cause of side effects.

When drug toxicity is evident, even in the presence of a low serum concentration, pharmacodynamic alterations may be the explanation. Likewise, a failure to respond to a medication at usual doses may imply altered PD for that medication in a particular individual. What is often seen clinically is that very elderly patients become very sensitive to drug actions, and the increased sensitivity is frequently exhibited as adverse effects. A prime example of this is the anticholinergic side effects of many medications that may appear as mental confusion in an elderly person. This is because the aged brain becomes more sensitive to anticholinergic effects. Another example is orthostatic hypotension from diuretic therapy. Normally, baroreceptors respond by instantly increasing vasoconstriction to maintain a stable BP, but in many elderly the baroreceptors are less functional, resulting in a precipitous drop in BP. This often results in the person falling and increasing his or her risk of fracturing bones. Pharmacodynamic differences do occur as a result of aging. Many of the pharmacodynamic alterations are directly responsible for an increased proportion of ADEs in older people and exaggerated or blunted clinical responses. More research on the effects of aging and drug response is urgently needed. Until we have a better understanding of pharmacodynamic alterations in aging, vigilant monitoring of therapeutic and adverse outcomes is mandatory in elderly patients.

Inappropriate Medication Use in Older People

In 1991 a group of researchers developed criteria that identified inappropriate medication use in nursing facility residents, including the frail elderly.[18] The criteria were established by using a consensus approach among a group of geriatric pharmacotherapy experts. The intent of developing this list was to use it both as a research tool to evaluate prescribing and drug utilization and for educational purposes. Medications were considered inappropriate if there was evidence in the literature to substantiate that the risk of drug use outweighed the clinical benefit when alternative therapy was available. The medications also were considered inappropriate if there was consensus among the expert panel—in the absence of published studies—that the risk of drug therapy was too high. The lead author on this publication was Mark Beers, MD, and these criteria are frequently referred to as the Beers criteria or the Beers list.[18]

Many researchers began using these explicit criteria in a variety of clinical settings soon after they were published.[19-27] Since the intent of the criteria was to

determine inappropriate prescribing only for nursing facility residents, revised criteria were published in 1997 that were intended to apply to any setting of care for elderly people.[28] These revised criteria contained a list of medications and medication classes that generally should be considered potentially inappropriate in older people and a list of medications that should be avoided in common medical conditions found in elderly patients. The Beers criteria have been incorporated into federal regulations.

More recently, updated Beers criteria were published in 2003.[29] As in previous iterations of the Beers criteria, this update used a consensus method among geriatric pharmacotherapy experts to generate lists of medications that, under most circumstances, should be avoided in older patients. The criteria were developed for the following situations:

"Medications or medication classes that should generally be avoided in persons 65 years of age or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available.

Medications that should not be used in older persons known to have specific medical conditions."[29]

These most recent Beers criteria contain 48 medications or medication classes that should be avoided in geriatric patients, and it gives the reasoning behind the decision to include the medications in the list. The criteria also specify if the adverse outcomes from using one of the medications on the inappropriate list are likely to have a high or low severity. In addition, these criteria specify 20 medical conditions, and medications that should not be used in these conditions.

Table 4 identifies selected medications from the current Beers criteria along with rationales for their being on the list. All health care providers who work with older adults should read the complete article and have this valuable resource readily available. The criteria can be downloaded free of charge from the *Archives of Internal Medicine* (Arch Intern Med 2003;163:2716-24 [www.archinternmed.com]).

One example of a medication that is listed by the Beers criteria as potentially inappropriate is amitriptyline. Although this antidepressant is effective, pharmacodynamic alterations seen in aging make it a less desirable agent. It possesses strong anticholinergic side effects, such as dry mouth, urinary retention, dry eyes, and constipation, which are exacerbated in older people. Many older people have dry eyes and dry mouth as a consequence of normal aging, and these problems get worse from medications possessing anticholinergic properties. In addition, amitriptyline is highly sedating, which can impair activities of daily living for seniors. Today, there are many effective selective serotonin-reuptake inhibitors (SSRIs) that are very effective antidepressants and do not have the adverse effects of older agents like amitriptyline. However, there may be clinical situations, such as neuropathic pain, when selecting amitriptyline may be appropriate.

Another example of why certain medications are included in the Beers criteria is the benzodiazepines. In the 2002 Beers criteria, short-acting benzodiazepines are listed as potentially inappropriate for older patients because of the increased sensitivity older patients have to the CNS effects; however, the criteria do provide doses to use for these agents when needed. Long-acting benzodiazepines, such as diazepam, are included in the Beers criteria because of their prolonged actions and the resulting sedation and increased risk of falling and fracturing bones. Often, safer alternatives are available to substitute for long-acting benzodiazepines.

For all the medications listed in the Beers criteria, better therapeutic options exist. For example, acetaminophen can be used instead of propoxyphene; the newer hypnotic agents are safer than flurazepam, and the second-generation sulfonylureas are much safer than chlorpropamide. Morphine, oxycodone, and other narcotic analgesics are better choices than meperidine in older people.

Many studies have been conducted using the first two versions of the Beers criteria to assess potentially inappropriate prescribing in a variety of settings. Table 5 identifies some of these studies. What is readily apparent from reviewing the table is that despite publishing three versions of the Beers criteria in a medical journal with a large circulation, little has changed over the past decade in prescribing habits. The rate of using potentially inappropriate medications in older people remains too high. Many prescribers argue that they have been using medications on the Beers list of inappropriate medications for years without negative consequences to their patients. However, because the adverse events of many of these medications are subtle, they often go unrecognized or get attributed to old age or the onset of new disease.

Table 4. Selected Medications from the 2002 Beers Criteria That Are Potentially Inappropriate in Elderly Patients

Medication or Medication Class	Rationale
Propoxyphene	Equally effective as other analgesics and has potential for narcotic-like adverse effects.
Muscle relaxants	Poorly tolerated because of anticholinergic side effects and sedation at effective doses.
Flurazepam	Extremely long half-life in the elderly causing prolonged sedation, falls, and fractures. Better sleep agents are available.
Amitriptyline	High anticholinergic and sedative effects. Rarely the medication of choice in an older person. Safer antidepressants are available.
Short-acting benzodiazepines	Increased CNS sensitivity in older people; smaller doses should be used.
Long-acting benzodiazepines	Prolong half-life in older people leading to increased risk of sedation, falling, and fractures. Short- or intermediate-acting benzodiazepines are preferred.
Digoxin at doses > 0.125 mg/day, except for arrhythmias	Decreased renal elimination in older people, which increases the risk of toxicity.
Chlorpropamide	Prolonged half-life in the elderly that can cause severe hypoglycemia.
Gastrointestinal antispasmodics	Severe anticholinergic side effects.
Diphenhydramine	Anticholinergic side effects and may cause confusion and delirium in older people. A poor choice as a hypnotic but can be used in treatment of acute allergic reactions.
Meperidine	Not very effective orally and may cause confusion.
Cimetidine	Potential for causing confusion.

Abbreviation: CNS = Central nervous system.
Source: Reference 29.

For example, NSAIDs are commonly used in older people and are available as prescription and nonprescription medications. A pharmacodynamic finding in elderly patients that does not occur in younger adults taking NSAIDs is memory loss, confusion, and other abnormal mental-status findings.[30,31] Older patients may experience these side effects and not tell anyone, thinking they are developing dementia. Likewise, even if they do report memory loss, health care providers may also attribute memory loss to dementia and not drug therapy.

Recommending alternative therapy for a patient prescribed a medication from the Beers criteria can be challenging. It is often difficult to convince a prescriber to use alternative therapy, and many times it is the patient who insists on using the medication, including nonprescription medications, such as diphenhydramine. Keep in mind that many elderly patients who use medications that are deemed inappropriate do well on them. Perhaps what is more important than using the list as an absolute contraindication for drug use is to frequently monitor patients using a Beers medication. Monitoring for the known adverse events that can be subtle can prevent more serious consequences to the patient.

Although we know that expert opinion and clinical trials suggest that the medications listed in the Beers criteria have a potentially unnecessary risk for use, there

Table 5. Selected Research Studies Assessing Potentially Inappropriate Prescribing in Older Patients

Author, Year*	Reference	Clinical Setting	Inappropriate Use† (%)
Beers, 1992	19	Nursing facility	40.0
Willcox, 1994	20	Community dwelling	23.5
Stuck, 1994	21	Community dwelling	14.0
Golden, 1999	22	Frail homebound	39.7
Fick, 2001	23	Managed care, outpatient	24.2
Zhan, 2001	24	Community dwelling	21.3
Gray, 2003	25	Residential care	22.0
Curtis, 2004	26	PBM, outpatients	21.0
Simon, 2005	27	HMO	28.8

* First author and year of publication.
† Use of one or more medications deemed potentially inappropriate by authors.
Abbreviations: HMO = Health maintenance organization members, PBM = Pharmacy benefits management enrollees.
Source: References 19-27.

are little data available for many of the medications on the list that clearly identify harmful outcomes from their use. Recently there have been a few published studies demonstrating that harm does occur from using a Beers criteria medication. One study showed that patients using potentially inappropriate medication as defined by the Beers criteria had greater hospitalization rates and had a greater chance of death compared with patients not receiving potentially inappropriate medication.[32] Another study examined adverse outcomes from Beers criteria medications in nursing facility residents.[33] This study showed that using medications on the Beers criteria list leads to increased rates of hospitalization, emergency department visits, and death. In a Medicare managed care plan, elderly patients receiving a Beers criteria medication had higher total health care costs, and more inpatient, outpatient, and emergency department visits than did comparable patients not receiving inappropriate medication.[23] All the studies examining outcomes from using Beers criteria medications are retrospective. These studies show an association between a medication's use and an outcome, but a true cause and effect is only suggested, not proven. Prospective clinical trials measuring positive and negative outcomes from using potentially inappropriate medications in elderly patients are desperately needed.

Summary

The first of the baby boomers will become 65 years old in a few short years, expanding the older population at unparalleled rates over the coming decades. Because older adults consume the largest number of prescription and nonprescription medications, problems associated with medication use will expand at unparalleled rates; therefore, practitioners must be even more attentive to appropriate medication use. ADEs in older people are common, and they are responsible for doctor office visits, hospitalizations, additional drug therapy—and sometimes death. Many of the ADEs are the result of alterations in PK and PD seen in elderly people. The effects of these alterations can be minimized if health care providers are cognizant of them and compensate by using lower doses of selected medications. When appropriate, providers should consider using alternative therapies that are likely to be better tolerated. The Beers criteria have evolved as a mechanism to help prescribers and others avoid using medications that may be inappropriate for the majority of older patients. Using these guidelines should help diminish unwanted ADEs. The criteria will be required to be periodically updated as new research comes to the forefront and new medications find their way to the marketplace.

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