

Inappropriate Medications for Elderly Patients

DARRYL S. CHUTKA, MD; PAUL Y. TAKAHASHI, MD; AND ROBERT W. HOEL, BS PHARM, RPH

The use of medications is common in elderly persons, and this population has the highest risk of medication-related problems. Elderly persons are more susceptible to the effects of various medications for a number of reasons. It is well known that polypharmacy is one of the most serious problems in caring for elderly persons; however, many of these patients continue to receive medications that have an increased risk of causing harm. In 1991, an important article was published about inappropriate medication use in the elderly population. This article raised awareness of the problem and presented explicit criteria for determining which medications were inappropriate for elderly patients residing in long-term care facilities. This list of drugs is still used for evaluating medications taken by elderly persons and for determining whether satisfactory prescribing practices are being used. We reviewed the medi-

cations described as inappropriate for elderly persons and searched the scientific literature to determine whether evidence exists to defend or refute the labeling of particular drugs. At times, evidence was difficult to find, and many of the original studies were dated. For most medications listed as inappropriate, we found evidence to support these designations.

Mayo Clin Proc. 2004;79:122-139

AV = atrioventricular; CHF = congestive heart failure; CNS = central nervous system; COX-2 = cyclooxygenase 2; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; OBRA = Omnibus Budget Reconciliation Act; REM = rapid eye movement; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; UKPDS = United Kingdom Prospective Diabetes Study

Although elderly persons represent only 12% of the US population, they receive a disproportionately large number of medications compared with younger individuals.¹ Medication use is highest in elderly persons who are institutionalized, with the typical resident in a long-term care facility receiving slightly more than 7 different medications per day. This is nearly double the rate of medication use in the independent elderly population. Not surprisingly, those living in long-term care facilities often are extremely ill and frail. They frequently require multiple medications to treat their complex set of medical problems. Medications necessary for managing medical conditions can put elderly individuals at risk of medication-induced problems such as adverse drug effects, drug-drug interactions, or drug toxicities.² These problems are more likely in elderly patients, in part because of age-related changes in pharmacokinetics and pharmacodynamics, reduced organ reserve capacity, multiple medical conditions, and the number of medications taken. Evidence indicates that physicians often prescribe medications that have an increased potential for causing harm to elderly patients.^{3,4}

Polypharmacy, a term commonly associated with physicians' prescribing tendencies for the elderly population, describes patients who receive many medications. Although the term carries a negative connotation, use of numerous medications in some elderly patients is frequently necessary.^{5,6} There are several legitimate reasons why elderly patients may receive numerous medications. Today, individuals have longer life expectancies than ever before, and as these persons age, chronic disease states often accumulate. Medical science continues to find new and better ways to manage chronic diseases. Until recently, physicians had few alternatives to offer patients with diseases such as osteoporosis, hyperlipidemia, or Alzheimer disease. Available treatment options were often minimally effective. Today, several pharmacological treatments are available for patients with these conditions, and despite the patient's age, many physicians are treating these conditions aggressively.

Although all medications have some risk of causing adverse effects, some medications have been identified as having a considerably higher potential to cause problems when prescribed to elderly patients. There are several reasons for this. Medication effects depend on how the body handles the drug (pharmacokinetics) and on how various target organs respond to the drug (pharmacodynamics). Both pharmacokinetic and pharmacodynamic changes occur with aging, frequently resulting in drugs having prolonged durations of activity, greater risks of toxicity, increased frequencies of adverse effects, and greater or lesser effects than anticipated from a given dose.

From the Division of Preventive and Occupational Medicine and Internal Medicine (D.S.C.), Division of Community Internal Medicine (P.Y.T.), and Hospital Pharmacy Services (R.W.H.), Mayo Clinic College of Medicine, Rochester, Minn.

Individual reprints of this article are not available. The entire Symposium on Geriatrics will be available for purchase as a bound booklet from the *Proceedings* Editorial Office at a later date.

Adverse reactions from medications are up to 7 times more common in persons aged 70 to 79 years than in those aged 20 to 29 years.² The greater the number of medications taken, the greater the risk of a clinically serious drug-drug interaction.⁷ Adverse drug reactions experienced by elderly patients often tend to be more severe than those experienced by younger patients. The reduced organ reserve capacity of elderly persons contributes to this. Essentially every organ system loses reserve capacity with age. Although a given organ usually has adequate capacity to function without stress, adverse effects may develop when that organ is stressed from a drug.

Medical prescribing for the elderly population can lead to serious complications. Nearly 5% of all hospital admissions are believed to be related to adverse drug reactions,⁸ and some studies report a rate as high as 17% for elderly persons.²

Many patients assume that only prescription drugs have risks of adverse reactions, but over-the-counter medications also have potential risk. Most drug-related adverse effects (80%) are due to prescription medications; however, the remainder are due to over-the-counter drugs. The risk of an adverse drug reaction increases with every new drug added to the treatment regimen.⁹ The risk of a patient having a clinically serious adverse drug reaction is estimated at 4 per 100 prescriptions; of these patients, 1 in 1000 will die from the reaction.¹⁰ Up to 140,000 deaths per year may be due to adverse drug reactions.¹¹

Symptoms of an adverse drug reaction 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. Because these problems are commonly seen in elderly persons, it is not uncommon for a physician to "treat" an adverse drug effect with another drug.

DEFINITION OF PROBLEM

Physicians have been criticized for their prescribing tendencies for elderly patients. Because of widespread and often excessive use of psychotropic medications in long-term care residents, federal legislation was developed to decrease the use of these drugs, improve documentation for appropriate use, and produce more effective monitoring of drug-related adverse effects.

Many medications that have an increased tendency to cause problems for older patients have been labeled as inappropriate drugs for this segment of the population. Recently, additional regulations have been developed for nursing homes regarding the use of inappropriate medications. Until recently, up to 40% of long-term care residents were receiving 1 or more inappropriate medications as part

of their treatment regimen.^{12,13} Data on elderly persons living in the community are more difficult to obtain; however, some studies indicated that 14% to 23.5% of elderly patients were receiving at least 1 inappropriate drug.^{14,15} Older patients and those for whom multiple medications are prescribed appear to be at greatest risk of receiving an inappropriate medication.

Possibly, the relatively high frequency of inappropriate drug use is related to pharmacoeconomic issues.¹⁶ Most drugs labeled as inappropriate tend to be older, less costly medications. For most inappropriate drugs, there are alternative products that accomplish the same effect with a greater margin of safety. These alternative drugs tend to cost substantially more; however, it could be argued that spending more initially for a safer drug would save money if serious adverse effects or hospitalization could be avoided.

The simplest definition of an inappropriate drug is one that has greater potential to harm than to benefit the patient. It is difficult to state that any given drug should not be used in an elderly patient under any circumstances. High-risk medications do not cause problems in all elderly patients, but they do have an increased potential to cause problems. In 1991 and 1992, important articles by Beers et al^{12,17} described inappropriate medications for nursing home residents. A group of 13 nationally recognized experts in geriatric pharmacology came to a consensus and provided explicit criteria for defining inappropriate use of medications in nursing home populations. The experts identified medications they believed should not be prescribed to elderly persons and other drugs for which doses, frequencies, or durations of use should not be exceeded. They also described medications that should be avoided in patients known to have various medical conditions. The original criteria were written for elderly persons who were institutionalized.

The recommendations were updated by a consensus panel of 6 nationally recognized experts in geriatric pharmacology in a 1997 article.¹⁸ The panel developed 28 criteria for classifying potentially inappropriate medications for the general elderly population and 35 criteria for classifying these medications for elderly patients having any of 15 different medical conditions. Because inappropriate medication use in nursing home residents was believed to be so prevalent, the Health Care Financing Administration essentially adopted the published list of inappropriate medications as guidelines for surveyors of long-term care institutions.

Defining what constitutes an inappropriate drug can be difficult. Beers et al¹⁷ developed the following criteria for classifying a drug as inappropriate for use in elderly patients:

- Specific medications or classes of medications that should not be used routinely in elderly persons. This may be due to lack of proven drug effect, a high likelihood of

Table 1. Anticholinergic Effects

Central nervous system	Drowsiness, fatigue, restlessness, irritability, disorientation, delirium
Eyes	Mydriasis, blurred vision secondary to paralysis of accommodation, obstruction of aqueous humor flow into trabeculae in persons with narrow anterior chambers
Heart	Tachycardia
Respiratory tract	Inhibited secretions of the nose, pharynx, and bronchi resulting in dry respiratory mucous membranes, decreased mucociliary clearance
Gastrointestinal tract	Inhibited salivary gland secretion; slowed gastric, small intestine, and colon motility; decreased gastric secretions; mild antispasmodic effect on biliary tract
Urinary tract	Decreased tone and amplitude of detrusor contractions
Sweat glands	Inhibited activity

adverse drug effects, the potential for severe adverse effects, or a high potential for interaction with another drug or class of drugs.

- Specific medications or classes of medications that should not be used routinely in elderly persons with specific disease states. Some drugs pose an increased risk for selected individuals with various medical conditions.
- Specific medications that have a risk of producing a serious adverse effect when safer alternatives are available. Many drugs considered inappropriate for use in the elderly population have alternatives with similar effects but a greater safety profile.
- Excessive dosages of medications used in elderly patients. Some medications for elderly patients are safe when used in lower doses but increase the risk of problems when used in higher doses.
- Excessive dosing frequencies that would make compliance difficult for elderly patients. Because elderly patients tend to take multiple medications, it is best to prescribe medications that have once-daily dosing when possible.
- Extended duration of use of medications that were intended to be used for a limited time. Some medications, prescribed initially for a limited time, become unnecessary and therefore inappropriate if taken long-term.

We reviewed the list of inappropriate drugs from the “explicit criteria” published by Beers.¹⁸ Our goal was to examine the evidence supporting the guidelines for those drugs used most commonly in the elderly population. Specifically, we looked for randomized controlled studies of drug effectiveness and whether elderly patients were included in the studies; this information was often difficult to find. We reviewed studies that objectively reported adverse effects because adverse effects were the basis for the Beers criteria. We considered the presence of adverse effects with use of any medication as important in the studies, but

adverse effects were of particular concern if the effectiveness of the agent was questionable or if the drug was used routinely for indications not well supported by controlled studies.

Controlled studies done before the 1990s often excluded elderly persons. Because of this, case studies and consensus of experts often appeared to be the main source of support for the guidelines.

ANTICHOLINERGIC DRUGS

Many drugs considered inappropriate for elderly persons produce anticholinergic effects. Often, these effects tend to be no more than a nuisance, although at times they can be rather serious.¹⁹ Early effects from anticholinergic drugs include dry mouth²⁰ and impaired diaphoresis. Moderate symptoms include increased thirst, tachycardia, and pupillary dilation. Anticholinergic toxicity can include urinary retention, agitation, hallucinations, seizures, cardiac arrhythmias, and heart block.²¹ Postoperative delirium has been reported in elderly patients taking anticholinergic drugs.²² Cognitive impairment also may occur. If used in patients with closed-angle glaucoma, these drugs substantially increase intraocular pressure that may threaten vision if not treated urgently.²³ Anticholinergic toxicity occurs more often when 2 or more anticholinergic drugs are taken together.²⁴

Elderly persons taking medications that produce anticholinergic effects are at increased risk of developing heat-stroke during times of increased environmental temperatures.²⁵ Thermoregulation is primarily controlled through cholinergic innervation of sweat glands and cutaneous blood flow. Anticholinergic medications inhibit diaphoresis, and this can occur at relatively low doses.²⁶ This effect has been seen with antiparkinsonian drugs that have atropine-like activity, tricyclic antidepressants (TCAs), phenothiazines, and antihistamines. Phenothiazines also disrupt thermoregulatory activity by affecting the hypothalamus (Table 1).

Occasionally, anticholinergic drugs are prescribed intentionally for elderly patients, for example, for overactive bladder, which becomes more common with increased age. Cholinergic innervation supplies the urinary bladder; to decrease premature detrusor contractions, an anticholinergic drug such as oxybutynin or tolterodine often is prescribed.²⁶

Although most of the literature involving anticholinergic drugs is dated, ample evidence suggests that most medications with anticholinergic activity should be avoided by elderly patients, with some exceptions.

- Many medications often prescribed to elderly patients have anticholinergic properties.
- Most anticholinergic drugs produce nuisance effects (eg, dry mouth, constipation, blurred vision), although some

effects may be serious (hypotension, cardiac arrhythmias, urinary retention, confusion).

- Most medications that produce anticholinergic activity should be considered inappropriate for the elderly population.

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants have been shown to be effective for treating depression in patients of all ages. The absorption, distribution, and elimination of TCAs vary extensively from one person to another. These drugs have high lipid solubility. In the elderly population, TCAs have an increased volume of distribution due to age-related pharmacokinetic changes. They also tend to bind extensively to plasma proteins. Metabolism varies 10- to 30-fold from one individual to another,²⁷ and elimination of TCAs slows with age. As a result, elderly patients who receive typical doses of TCAs usually develop higher plasma drug levels and metabolites than do younger patients. All TCAs produce various degrees of anticholinergic activity and frequently cause problems in elderly patients. The tertiary amines, including amitriptyline, imipramine, and doxepin, produce a greater amount of anticholinergic activity than the secondary amines nortriptyline and desipramine.²⁸ If use of a TCA is necessary, nortriptyline and desipramine are preferred agents for elderly patients.

Cardiac toxicity, the most serious complication from TCAs, is more likely to occur in persons with preexisting cardiac disease.²⁹ Cardiac symptoms can occur with any of the TCAs and are more likely with higher blood levels (eg, overdoses). Tricyclic antidepressants can slow intraventricular conduction and can produce 2:1 or 3:1 heart block and complete heart block. Persons with preexisting cardiac conduction delay are at increased risk.^{30,31} Like quinidine, TCAs produce antiarrhythmic activity and often suppress ventricular ectopy. Also like quinidine, TCAs produce proarrhythmic activity and can cause ventricular arrhythmias, which may be fatal. When this occurs, it is often early in the course of treatment. An association has been found between sudden death and use of amitriptyline in patients with a history of cardiac disease.²⁵

The most common potentially serious adverse effect from TCAs is orthostatic hypotension,³¹ which becomes more common with advancing age and can occur even when these drugs are used in low doses.²⁹ Orthostatic hypotension, caused by the α -1 adrenoceptor antagonist activity of TCAs, increases the risk of falls and fractures in elderly patients.³² An orthostatic blood pressure level decrease greater than 10 to 15 mm Hg before initiation of TCA therapy is associated with an increased risk of symptomatic orthostatic hypotension once TCA therapy has begun.³¹ The risk of orthostatic hypotension is less with nortriptyline.²⁹

Table 2. Commonly Prescribed Antidepressants*

	Effects		
	Sedation	Hypotension	Anticholinergic
Amitriptyline	+3	+3	+3
Doxepin	+3	+2	+2
Imipramine	+2	+2	+2
Nortriptyline	+1	+1	+1
Desipramine	0/+1	+1	+1
Fluoxetine	0/+1	0	0
Paroxetine	0/+1	0	0/+1
Sertraline	0/+1	0	0

*Numbers indicate potential for listed effects: 0 (none) through +3 (high).

Tricyclic antidepressants also can cause central nervous system (CNS) effects such as confusion and seizures, which occur more commonly in elderly persons. Cognitive impairment tends to be worse in those with some degree of underlying dementia. Use of TCAs also can be associated with gastrointestinal (GI) and urinary effects. As a result of the anticholinergic effect, gut motility can decrease, leading to constipation problems.³³ Impairment of urinary bladder contraction can result, producing urinary retention. Tricyclic antidepressants can increase intraocular pressure and should not be used in patients with closed-angle glaucoma (Table 2).

Medication studies from the 1990s of nursing home residents showed common use of sedative/hypnotics³⁴ and antipsychotics.³⁵ The use of antidepressants was relatively low, ranging from 6% to 16%,³⁶ which may have reflected a lack of recognition of depression in this group of patients but more likely was a result of the respect for the potentially serious adverse effects of the older TCAs. More recent studies have indicated an increased frequency of antidepressant use in elderly patients in nursing homes. Current rates of treatment with antidepressant drugs in nursing home residents are as high as 30%,³⁷ probably in part due to the availability of safer and better-tolerated antidepressant medications. Currently, selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressant medications in both general medical and psychiatric practices.³⁸

One indication that remains for use of TCAs is the treatment of neuropathic pain; SSRIs have shown no benefit for this problem. Generally, the TCA doses used for neuropathic pain are much lower than those used for treating depression.

Tricyclic antidepressants have antihistamine effects and sedating properties. Although these effects are undesirable when they cause daytime drowsiness, they may be useful occasionally for persons with insomnia due to depression. Because SSRIs typically are nonsedating, insomnia may be a problem until the depression improves.

The literature contains ample evidence that TCAs should be designated as potentially inappropriate for elderly patients. Currently, there is little reason to prescribe traditional TCAs to treat depression in the elderly population because considerably safer products with similar efficacy are available.

- Tricyclic antidepressants are effective for managing depression.
- Most TCAs produce notable anticholinergic effects.
- Although many adverse effects of TCAs are not serious, others such as cardiac arrhythmia, hypotension, confusion, and urinary retention can be dangerous.
- Antidepressants with efficacy similar to TCAs but with fewer adverse effects are available and should be used in place of TCAs.

ANTIPSYCHOTIC MEDICATIONS

Antipsychotic medications are prescribed occasionally to elderly patients to help manage behaviors associated with dementia.³⁹ Although not specifically indicated for this purpose, they have the potential to improve behaviors such as paranoia, agitation, hallucinations, and delusions, commonly associated with dementia. They have shown no usefulness in managing wandering, pacing, or repetitive vocalizations. These drugs have been commonly,⁴⁰ and at times inappropriately, prescribed to nursing home residents.³⁶ Although antipsychotic medications can be effective in managing behavior disturbances, they often produce adverse drug effects in elderly patients because of the specific effects of the drug (described in the next paragraph) and the pharmacokinetic and pharmacodynamic changes associated with aging.

Adverse effects of antipsychotic medications include typical anticholinergic effects (dry mouth, constipation, blurred vision, urinary retention, and cognitive impairment) and extrapyramidal symptoms (bradykinesia, stiffness, cogwheel rigidity, akinesia, and akathisia). Extrapyramidal symptoms are more common in elderly patients than in younger ones and continue for longer periods once the antipsychotic medication has been discontinued.²⁰ It has not been uncommon for practitioners to treat extrapyramidal effects with anticholinergic antiparkinsonian medications.⁴¹ This practice can result in excessive anticholinergic activity in these patients. Tardive dyskinesia also can occur from use of antipsychotic drugs and is more common in elderly patients after even a relatively brief exposure to these drugs.²⁰ Other common adverse effects produced by antipsychotic medications include excessive sedation, orthostatic hypotension, and increased risk of falls⁴² and hip fractures.²⁷ Many antipsychotic medications have quinidine-like effects, similar to TCAs. They can prolong cardiac conduction and have the potential to produce cardiac

arrhythmias. All these adverse effects tend to occur more commonly in elderly patients and at lower doses than are used in younger patients. Antipsychotic drug use in elderly patients with dementia can further impair cognitive function; this effect is likely secondary to the anticholinergic effects of these medications that further impair an already impaired cholinergic system.²⁸

Until recently, reports were common of excessive use of psychotropic medication in nursing homes that often involved misdiagnosis and inadequate monitoring of patients taking these medications. As a result, the 1987 Omnibus Budget Reconciliation Act (OBRA) produced major reforms in the use of antipsychotic medications in nursing homes. It led to regulations that dramatically changed prescribing practices for antipsychotic medications,⁴³ and the use of taken-as-needed antipsychotic medications decreased. Researchers estimated that if OBRA regulations regarding the use of antipsychotic medications had been in effect from 1976 to 1985, approximately half of all antipsychotic drug use would have been considered inappropriate.⁴⁴ OBRA regulations also resulted in improved documentation for the use of antipsychotic drugs and the use of minimal effective dosing for elderly patients in nursing homes.⁴⁵

In the past few years, several new neuroleptic or “atypical” antipsychotic medications have been introduced with considerably improved safety profiles compared with those of typical antipsychotic medications. Clozapine was the first atypical antipsychotic; after a brief period of use, the drug was found to occasionally produce agranulocytosis. Other atypical antipsychotic medications, including risperidone, olanzapine, and quetiapine, are associated with notably fewer extrapyramidal effects and much less potential to produce tardive dyskinesia. Although the atypical antipsychotic medications are superior to the traditional antipsychotics in terms of safety, they appear to have similar efficacy.⁴⁶ Evidence suggests that currently physicians are preferentially prescribing these newer-generation antipsychotic medications for nursing home residents.⁴⁷

The literature contains ample evidence that traditional antipsychotic medications are potentially inappropriate for elderly patients. Beers¹⁸ recommended dosage limitations for both haloperidol and thioridazine. Currently, there is little reason to prescribe traditional antipsychotics to elderly patients because considerably safer products with similar efficacies are available.

- Antipsychotic medications are occasionally prescribed to elderly patients, especially those with behavior problems associated with dementia.
- The traditional antipsychotics produce either anticholinergic effects or have the potential to produce extrapyramidal effects.

- Tardive dyskinesia represents the most serious adverse effect from antipsychotic medications and can occur in elderly persons after short-term use and low doses.
- New-generation antipsychotic medications are available with efficacy similar to traditional antipsychotics and with a greater safety record.
- Older antipsychotic medications should be considered inappropriate for elderly patients.

BARBITURATES

Barbiturates have been available for many years and are prescribed for various reasons. They have sedative, anesthetic, anxiolytic, and anticonvulsant properties.⁴⁸ Barbiturates engage the γ -aminobutyric acid receptor within the brain, resulting in sedative and hypnotic effects and an elevation of the seizure threshold.⁴⁹ Before the availability of benzodiazepines, barbiturates were used widely as anxiolytics and sedatives. They are not an ideal choice as a sedative/hypnotic for elderly patients. All barbiturates are highly lipid-soluble drugs, and because of the increased adipose tissue occurring with aging, there is an increased volume of distribution for barbiturates. This often results in an increased drug half-life and prolonged duration of action for this class of drugs. Even secobarbital, the least lipid-soluble of the barbiturates, has an excessively long half-life that can result in drug accumulation producing daytime drowsiness.

Although barbiturates decrease sleep latency and therefore reduce the time required for individuals to fall asleep, the sleep is not normal. Barbiturates suppress rapid eye movement (REM) sleep, and many persons who take this drug do not feel rested when they awaken the next morning. If the barbiturate is discontinued, the patient experiences a REM rebound, with their sleep interrupted often by unpleasant dreams. Tolerance to the sedating activity of barbiturates develops often, and a larger dose is required frequently to produce continued sedation. Barbiturates are used occasionally as an anticonvulsant for those with a history of seizures. They are relatively low-cost drugs, and the sedation they produce is usually transient.

In elderly patients, barbiturates produce many undesirable adverse effects, some of which are due to drug-drug interactions. Barbiturates induce cytochrome P-450 enzymes, which metabolize other drugs; this often results in inappropriately low levels of other medications that are hepatically degraded. Alterations in hepatic metabolism of these drugs with aging can produce undesirable adverse effects.⁵⁰ Although there is considerable variability among individuals, in general, hepatic metabolism decreases with age. Thus, there are marked increases in barbiturate levels for many elderly persons, which can result in marked prolongation of activity for barbiturates.

As barbiturate levels increase in elderly patients, so does the potential for toxicity. Barbiturates in high doses may lead to respiratory depression or coma, which can be life threatening. Barbiturates also have an additive effect with alcohol that can lead to respiratory depression.⁵¹ Habituation occurs frequently with barbiturates. Patients can experience barbiturate withdrawal and withdrawal seizures when barbiturates are discontinued. This scenario can occur when a patient is hospitalized or is admitted to a short-term or long-term care facility.

Older patients should avoid barbiturates for reasons beyond direct toxicity, habituation, and drug interactions; the most concerning is the frequency of falls. The central effect of barbiturates results in anxiolytic properties, decreased attention, and sedation. The sedation and decreased attention increase the risk of falls,⁵² which frequently lead to fractures and increased mortality.⁵³

Ample evidence from the literature suggests barbiturates are potentially inappropriate for elderly patients. With the introduction of benzodiazepines, barbiturate use has decreased markedly; benzodiazepines are preferred to barbiturates for almost all uses. The prominent exception is use as an anticonvulsant; however, barbiturates should be used with caution even for this indication. With the availability of safer alternatives, barbiturate use in older patients should be limited.

- Barbiturates have been prescribed to elderly patients as both a sedative/hypnotic and an anticonvulsant.
- Because of their high lipid solubility, barbiturates tend to have a prolonged duration of activity in elderly persons and can easily lead to drug accumulation and toxicity.
- Tolerance to the sedating effects of barbiturates develops frequently, and often the sedative effect is short-lived.
- Barbiturates suppress REM sleep, resulting in unnatural sleep.
- Barbiturates should be considered as inappropriate for the elderly population in most circumstances (except as an anticonvulsant).

BENZODIAZEPINES

The introduction of benzodiazepines was a major improvement for the treatment of anxiety mood disorders. Benzodiazepines work on the γ -aminobutyric acid site within the CNS.⁵⁴ They have less effect on the respiratory system and maintain a much larger therapeutic window than do barbiturates.

Benzodiazepines are categorized according to half-life (primarily determined by their lipid solubility) and the presence or absence of active metabolites. The older benzodiazepines (diazepam, chlordiazepoxide, flurazepam) are highly lipid-soluble. Like barbiturates, they have an increased volume of distribution because adipose stores

tend to increase with age. This results in a substantial increase in drug half-life for lipid-soluble benzodiazepines. The half-lives of these products can increase by a factor of 4 to 5 for an 85-year-old patient compared with a 25-year-old patient. The half-life of diazepam for an 85-year-old patient can exceed 80 hours. Low lipid-soluble benzodiazepines include lorazepam and oxazepam. These compounds have short half-lives—both under 8 hours—and have much less risk for accumulation and toxicity in elderly patients.

Benzodiazepines undergo hepatic degradation and are cleared subsequently from the body. Although there is notable variability from one person to another, hepatic function generally decreases with age, and the half-life of benzodiazepines can increase. Because of pharmacokinetic and pharmacodynamic changes related to aging, elderly patients have a greater potential for experiencing effects from benzodiazepines, including excessive sedation.⁵⁵ Problems reported with benzodiazepine use in elderly patients include dependence, cognitive impairment, and increased risk of falls.^{56,57} Older patients show a response to a lower plasma level of benzodiazepines than do younger patients.⁵⁸

Prescribing long-acting benzodiazepines for elderly patients has been criticized. These drugs have been associated with falls and increased mortality. With the availability of safer short-acting or medium-acting benzodiazepines, there is little reason to use benzodiazepines with a long half-life. When possible, use of benzodiazepines as a class should be limited. However, when benzodiazepines are indicated for use in elderly patients, those drugs with low lipid solubility and without active metabolites should be preferentially prescribed. These drugs should be used in low doses and only for short-term use when possible.

Ample evidence in the literature suggests that long-acting benzodiazepines are potentially inappropriate for elderly patients.

- Benzodiazepines are effective sedative/hypnotic and antianxiety medications.
- Longer-acting benzodiazepines are highly lipid soluble with active metabolites, which result in a long duration of activity in elderly patients.
- Short-acting benzodiazepines have low lipid solubility and no active metabolites, which result in a short duration of activity in elderly patients; these drugs are preferred when a benzodiazepine is indicated in elderly patients.

MEPROBAMATE

Meprobamate is an older anxiolytic that has also been used as a muscle relaxant. Meprobamate produces habituation and leads to withdrawal symptoms and seizures when discontinued abruptly. Available evidence exists for classifying

ing meprobamate as a potentially inappropriate drug for the elderly population because benzodiazepines have similar efficacy and are safer than meprobamate.⁵⁹

ANTIHISTAMINES

Antihistamines have many useful applications and are used frequently. Antihistamines reduce the symptoms of atopic disease such as urticaria and allergic rhinitis; they are also sedating and induce sleep. Patients frequently take antihistamines as over-the-counter medications for insomnia, upper respiratory tract infection, or allergies. Physicians prescribe both traditional antihistamines and the newer nonsedating antihistamines in the clinic, hospital, and nursing home settings. Older antihistamines such as diphenhydramine are the primary agents that present risks for the elderly population. These first-generation antihistamines cross the blood-brain barrier, which subsequently causes sedative effects. This “adverse” effect is the primary reason for their use as hypnotic agents.^{60,61}

The older antihistamines, primarily diphenhydramine, cause many CNS adverse effects such as cognitive slowing⁵⁹ and delirium in older patients. This effect is more pronounced in elderly patients with some degree of preexisting cognitive impairment. The anticholinergic properties of older antihistamines produce effects such as dry mouth, constipation, blurred vision, and drowsiness. Thus, the use of antihistamines as sleeping agents or for symptomatic relief often leads to problems in elderly patients. The sedating effect of antihistamines can affect driving skills. Often, older patients have decreased vision and decreased motor reflexes as a result of either disease or age-related changes; the sedative effect of older antihistamines places these patients at even greater risk of injury from motor vehicle crashes.⁶² The sedative effects of older antihistamines also increases older patients’ risk of falls. Hip fractures and subsequent death have been reported in patients who use older antihistamines such as diphenhydramine.⁵³

Adequate evidence supports the designation of diphenhydramine as a potentially inappropriate medication for elderly patients. Patients with atopic illnesses such as urticaria or allergic rhinitis or those who have primary dermatologic problems should use a second-generation antihistamine. Antihistamines such as fexofenadine, loratadine, and cetirizine provide optimal antihistamine effect with no notable central effect. These medications do not increase the risk of injury from motor vehicle crashes or from falls or impair cognitive function in elderly patients.

- Older antihistamines such as diphenhydramine are often purchased over-the-counter to treat insomnia and the symptoms associated with allergies.
- Diphenhydramine often produces sedation and has the potential to cause cognitive impairment.

- When elderly patients need an antihistamine, newer products are available that do not produce drowsiness and should be used instead of diphenhydramine and the other older antihistamines.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) have antipyretic, anti-inflammatory, and analgesic properties. The analgesic and anti-inflammatory effects are mediated through 2 different mechanisms. NSAIDs inhibit cyclooxygenase, an enzyme required in the conversion of arachidonic acid to prostaglandins. This results in suppression of the inflammatory response and pain.²⁹ NSAIDs also inhibit the migration of neutrophils that are attracted to inflammation.⁶³ This results in a decreased release of free radicals and cytotoxic enzymes, blunting the inflammatory response. The high frequency of NSAID use in the elderly population is due to the high prevalence of chronically painful conditions such as osteoarthritis. NSAIDs do not affect the natural history of osteoarthritis or rheumatoid arthritis and are not considered disease-modifying drugs; they are used for symptom management only. Although NSAIDs provide the bulk of treatment for inflammatory musculoskeletal disorders, they also are prescribed frequently for noninflammatory conditions. There is little evidence to indicate that NSAIDs are superior to other analgesics without anti-inflammatory activity for these conditions.⁶⁴

Currently, up to 4% of all prescriptions filled are NSAIDs.⁶⁵ It is estimated that more than 1% of the US population use NSAIDs long-term. This percentage is even higher in the elderly population; an estimated 10% to 20% of those older than 65 years have a current or recent prescription for an NSAID.⁶⁵ Worldwide, more than 30 million patients receive prescriptions for NSAIDs daily.⁶⁶ Approximately half of all NSAID prescriptions are written for patients older than 60 years.⁶⁷

NSAIDs are highly lipid-soluble drugs with extensive protein binding. The high lipid solubility of NSAIDs results in their widespread distribution in elderly persons due to increased age-related adipose tissue stores. Elderly persons also have an increased concentration of unbound drug due to reductions in plasma protein found in many older persons. Since many elderly persons have reduced renal function, NSAIDs have decreased renal clearance in older patients, potentially resulting in excessive drug levels and toxicity.

Complications from NSAID use are well documented and can affect the GI, renal, cardiovascular, CNS, and hematologic systems. Adverse effects from NSAIDs are relatively common in the elderly population, in part because these drugs are used so extensively in this segment

of the population.⁶⁸ Adverse effects tend to be more severe in elderly than in younger persons. Disability, associated with advanced age and multiple disease, is associated with an increased frequency of hospitalizations due to GI complications in those taking NSAIDs. NSAID-induced gastropathy is the most common and severe adverse drug effect. Damage occurs as a result of both topical injury and a systemic effect through inhibition of prostaglandin synthesis. Even NSAIDs given rectally can produce gastric complications.⁶⁹

An estimated 15% to 35% of all peptic ulcer complications are secondary to NSAID use. Life-threatening complications from peptic ulceration are common. In the United States, NSAIDs result in an estimated 41,000 hospitalizations per year with a 2% to 4% annual incidence of serious GI complications (peptic ulceration, upper GI hemorrhage, perforation).⁷⁰ In addition to gastric and duodenal complications, NSAIDs can produce complications in the esophagus (ulceration, stricture), small intestine distal to the duodenum (hemorrhage, ulceration, malabsorption, perforation, stricture, inflammation), and colon (ulceration, hemorrhage, stricture, colitis).⁷¹⁻⁷³ A relatively high degree of lipid solubility of NSAIDs, potentially decreased plasma protein, and reduced renal function in elderly persons all contribute to pharmacokinetic effects, which increase the potential risks of NSAIDs.⁷⁴

Up to 20,000 patients die each year as a result of GI complications from NSAID therapy, 3000 of whom are elderly patients.⁷⁵ The risk of developing peptic ulcer complications from NSAID use increases with increasing age and dose.⁷⁶ Endoscopic studies have shown that when higher doses of NSAIDs are taken, there is a dose-response effect with greater mucosal injury and likelihood of ulceration. Patients taking NSAIDs and anticoagulants have a 12-fold increased risk of upper GI bleeding.⁷⁷ Those taking more than 10 mg/d of prednisone with an NSAID have a 7-fold increased risk for upper GI bleeding.⁷⁸

Many peptic ulcers due to NSAID use lack the typical symptoms, and patients present with serious upper GI bleeding or perforation. Up to 60% of individuals with mucosal erosions from NSAID therapy are asymptomatic.⁷⁹ Lack of symptoms associated with NSAID gastropathy is more common with advanced age. NSAIDs can increase blood pressure level, with an increase in mean arterial pressure averaging approximately 10 mm Hg.⁸⁰ This is more common in elderly patients. The effects of various antihypertensive agents, especially those whose action is via renal prostaglandins such as β -blockers and angiotensin-converting enzyme inhibitors, are blunted by NSAIDs. NSAIDs also can produce renal insufficiency (both acute renal failure and worsening of chronic renal insufficiency), hyperkalemia, and fluid retention.⁸¹

When treatment with an NSAID is indicated in elderly patients, the lowest effective dose should be used. Higher doses producing anti-inflammatory effects may not always be necessary. The need for the NSAID should be reviewed periodically. Also, a periodic check of the renal function of elderly patients using NSAIDs long-term is recommended.

Alternatives to NSAID therapy include acetaminophen, tramadol, nonacetylated salicylates, narcotics, intra-articular corticosteroids, and the cyclooxygenase 2 (COX-2) inhibitors.

Acetaminophen has been shown to be effective in the treatment of chronic pain from osteoarthritis. Up to 4 g/d is generally safe for elderly persons; however, caution must be used in prescribing to patients with any degree of hepatic disease and to those who ingest large quantities of alcohol.

Tramadol is a nonnarcotic analgesic that can be effective in controlling both acute and chronic pain. Tramadol does not have a notable degree of plasma protein binding. It does not elevate blood pressure levels or worsen congestive heart failure (CHF) and has no potential for GI toxicity. Tramadol may produce adverse GI effects including nausea and vomiting and can produce unsteadiness.⁸²

Nonacetylated salicylates have less potential for serious GI adverse effects than do other NSAIDs; however, most physicians believe that the efficacy in symptom management with these compounds is less.

Opioids bind to opiate receptors and produce relief of pain. One of the main limitations of opioids in chronic pain is the potential for tolerance to their analgesic activity. Other adverse effects include nausea, vomiting, and confusion. Physical dependence also can result from long-term use of opioids. This should not be a factor when opioids are used in patients with terminal illness. Misoprostol is a synthetic prostaglandin analogue. When combined with traditional NSAID therapy, it can reduce the risk of GI adverse effects.

For some patients, intra-articular corticosteroids should be considered as an alternative to long-term use of NSAIDs.

NSAIDs inhibit the production of prostaglandins by inhibiting the enzyme cyclooxygenase. Traditional NSAIDs inhibit both COX-1 and COX-2. Anti-inflammatory effects are due to the inhibition of COX-2, whereas the undesired adverse effects are due to the inhibition of COX-1. The newer NSAIDs have selectivity for COX-2 inhibition; they appear to have fewer adverse effects than traditional NSAIDs but have similar efficacy. The potential for renal toxicity from COX-2 inhibitors is similar to that of traditional NSAIDs.

These alternatives to traditional NSAIDs should be considered when prescribing for elderly patients with chronic pain. There can be considerable cost differences, especially

with the COX-2 inhibitors, and safety benefits must be weighed against this additional cost. When traditional NSAIDs are indicated for treating elderly patients, the lowest effective dose is recommended, especially when no inflammatory component is involved.

Beers¹⁸ did not address NSAIDs as a group but did indicate that several NSAIDs were potentially inappropriate for use in the elderly population. Indomethacin was singled out because of its CNS toxicity, and use of phenylbutazone was discouraged because of its risk of toxicity in bone marrow suppression. NSAIDs are believed to be inappropriate for elderly persons with a history of peptic ulcer disease and gastroesophageal reflux because of the drugs' potential to worsen these conditions.

Because of the extremely widespread use of NSAIDs in the elderly population, large numbers of serious adverse effects occur. However, because of the health problems common in elderly persons that result in chronic pain and because NSAIDs benefit so many people, these drugs will continue to be used. There is not adequate evidence to label the entire class of anti-inflammatory drugs as inappropriate for use by the elderly population. However, NSAIDs have considerable potential for serious adverse effects, especially when used long-term and in higher doses. Therefore, NSAIDs should be used judiciously and in low doses when possible or should be replaced with lower-risk alternatives. Patients receiving long-term therapy should be observed closely for adverse effects.

- NSAIDs are prescribed frequently to elderly persons and notably benefit those with painful conditions.
- NSAIDs have potential for serious GI, renal, and CNS effects.
- Because of the widespread use of NSAIDs in the elderly population, adverse effects from NSAIDs may appear to be extremely common.
- Adequate data are unavailable to label the class of NSAIDs as inappropriate for use in the elderly population.
- NSAIDs should be used judiciously and in low doses if possible by elderly persons.
- Alternatives to NSAIDs should be tried before giving elderly patients long-term NSAID therapy.

OPIATE-RELATED ANALGESICS

Within the Beers¹⁸ guidelines are recommendations to avoid the use of certain opiate-related analgesics, specifically pentazocine, propoxyphene, and meperidine, all of which have been available to clinicians for a relatively long time. Guidelines for the appropriate use of available analgesics are becoming more clearly defined but have developed slowly. Reasons for this are related partly to limitations of studies, particularly those from earlier decades. Subjective methodology and bias often have clouded the

objective measurement of analgesic efficacy. Initial trials comparing response of one analgesic to another or to placebo often involve a single dose or short-term therapy. Consequently, these methods report few adverse reactions, and adverse effect reporting was not an end point of many studies. This suggests that unpredicted problems may arise when these agents are given to patients long-term.

Pentazocine

Pentazocine is a mixed opiate agonist/antagonist marketed in the 1970s in the United States. It has been studied and prescribed more frequently in Europe. The disadvantages of pentazocine include its mixed agonist/antagonist activity. Seizures have been associated with its use, which have not been reported with other opiate analgesics. Also, pentazocine has been reported to cause more dysphoria than morphine.⁸³ Specific concerns about the safety of pentazocine in the elderly population have been raised in case reports describing psychotropic effects, specifically hallucinations^{84,85}; for this reason, its use in elderly persons has been termed inappropriate. Many, but not all, of these reported adverse effects occurred in patients taking unusually high doses.

Published trials have compared pentazocine with other analgesics such as tramadol, nalbuphine, meptazinol, butorphanol, and codeine. Randomized controlled studies were reviewed that compared injectable and/or oral pentazocine against placebo and the other narcotic analgesics and examined adverse effects as a major end point. These studies, some of which included patients between ages 65 and 75 years, all showed pentazocine to be effective. None noted an increased incidence of hallucinations, confusion, or other psychotropic effects in normal dosages. Drowsiness, sedation, and confusion are reported frequently in the studies but not more frequently with pentazocine than with other analgesics.⁸⁶⁻⁸⁹

In more recent studies comparing pentazocine to newer narcotic analgesics, frequent confusion from pentazocine was reported. However, examination of the adverse effects reported in these small trials often did not substantiate these findings.⁹⁰ In another study in which patients were given increased doses of up to 240 mg of pentazocine, CNS changes, specifically disordered thoughts and hallucinations, were reported in patients of all ages.⁹¹ We might extrapolate that with long-term use of pentazocine in patients with impaired elimination of the drug, accumulation may occur and result in hallucinations.

Although there is a scarcity of strong data documenting serious problems with pentazocine, some evidence indicates that the drug may increase the risk of adverse effects in elderly patients.⁸⁶ Other analgesics are available with

similar efficacy and theoretically have fewer adverse effects; therefore, it seems prudent to avoid the use of pentazocine in the elderly population.

- Pentazocine is a mixed opiate agonist/antagonist with analgesic activity.
- Published studies indicate adequate efficacy for pentazocine.
- Studies suggest a possible increased risk of seizures and CNS effects compared with other analgesics with similar efficacy.

Propoxyphene

Propoxyphene is an opioid narcotic that binds to receptors within the CNS to produce mild analgesia. It has essentially the same potential to produce the adverse effects typically seen with other opiates such as constipation, decreased balance, CNS depression, and cognitive impairment. Propoxyphene has an onset of action from 15 to 60 minutes and a time to peak effect of 2 hours. Its overall duration of effect is from 4 to 6 hours. The drug's primary metabolite, norpropoxyphene, is eliminated along with 10% of unchanged parent drug through the kidneys. The elimination half-life of propoxyphene is 6 to 12 hours, whereas that of norpropoxyphene is 30 to 36 hours. As renal function declines, elimination is substantially prolonged, and toxicity becomes more likely.

Considerable evidence suggests that propoxyphene may be less effective as an analgesic than acetaminophen, and in certain trials, propoxyphene did not statistically outperform placebo in treatment of pain.^{92,93} Also, propoxyphene napsylate with aspirin did not attain greater analgesia than aspirin.⁹⁴ Several trials have shown that NSAIDs such as diflunisal or ibuprofen may be as effective or more effective than propoxyphene in treating various pain-related problems.⁹⁵

Propoxyphene often is dispensed in combination with acetaminophen, which may account for most of its analgesic activity. To prevent potential toxicity, the total acetaminophen dose needs to be considered when patients take acetaminophen and the combination of propoxyphene and acetaminophen. Single doses of greater than 1 g are not recommended, nor are total daily doses greater than 4 g. This is especially important in patients with hepatic dysfunction or in those who ingest alcohol. Propoxyphene can interact with warfarin and potentiate the anticoagulant effect. It has been implicated in lowering the seizure threshold more than other opioid analgesics and can be hepatotoxic or cardiotoxic.

The risk of CNS toxicity is greater in elderly patients who exhibit slower clearance. Two large epidemiological studies that examined CNS toxicity and the subsequent risk of falls resulting in hip fractures linked propoxyphene to

impaired cognition and an increased risk of falls with associated hip fractures.^{96,97}

Propoxyphene provides limited analgesic benefits with risks of adverse effects equal to other narcotics. Adequate evidence supports the designation of propoxyphene as an inappropriate drug in the elderly population.

- Adverse effects from propoxyphene are similar to other narcotics that have greater analgesic effects.
- Propoxyphene is deemed inappropriate for elderly persons because of its doubtful efficacy compared with other less toxic analgesics.

Meperidine

Meperidine has been one of the most commonly prescribed parenteral narcotic analgesics and is used as an alternative to morphine. It is short-acting, is somewhat less constipating than other narcotic analgesics, and is used primarily to treat acute and severe postoperative pain. However, there are many indications for which meperidine has been listed as potentially useful. It has been used as an adjunct to both general anesthesia and preprocedural conscious sedation. It has been a mainstay of analgesia for labor pain and has been used as an alternative to morphine for pain relief related to myocardial infarction. Also, it has been used to treat headache, postoperative shivering, and rigors related to therapeutic infusions.

The reported equianalgesic dose of 10 mg of intramuscular morphine is 75 mg of intramuscular meperidine. Elderly patients reportedly have a higher incidence of adverse effects to meperidine, which can be attributed to previously discussed changes in physiology and pharmacokinetics. These include a measurably longer drug half-life, altered protein binding, and an increased volume of distribution reported to be 135% to 300% higher than that of younger patients. Higher serum levels of meperidine are reported in elderly persons compared with younger patients receiving equal doses.⁹⁸

The use of meperidine for chronic pain has been shown to increase the incidence of toxicity. Undesired effects include anxiety, tremors, myoclonus, and generalized seizures. Many adverse reactions have been attributed primarily to the accumulation of a major metabolite, normeperidine. Normeperidine has much weaker analgesic effects than its parent compound but much greater CNS toxicity.⁹⁹⁻¹⁰¹ The average half-life of meperidine is 2 to 3 hours; however, for normeperidine it is approximately 17 hours and increases in patients with impaired hepatic and/or renal function. The half-life of normeperidine may increase to 35 hours in patients with renal failure.¹⁰²

Oral meperidine has only about one quarter the analgesic effect of parenteral meperidine. However, because of

first-pass metabolic pathways related to oral use, equal amounts of its major metabolite normeperidine are generated.¹⁰³ The oral absorption of meperidine is extremely variable and unpredictable.

Because of toxicity and accumulation issues, particularly inherent in the elderly population, if meperidine is prescribed, the dose and duration of use should be limited carefully. When addressing analgesia in elderly persons, the agents that should be considered are those for which accumulation and/or metabolite toxicity would be less of an issue, such as hydromorphone, fentanyl, methadone, or morphine.

Adequate published information indicates increased risks of adverse effects from meperidine and supports the classification of meperidine as inappropriate for elderly patients. Numerous other analgesics have similar efficacy and fewer risks of adverse effects and toxicity.

- Although meperidine has been effective when used in younger individuals, pharmacokinetic and pharmacodynamic changes associated with aging result in substantial risks when the drug is used in elderly patients.
- Oral meperidine has one fourth the analgesic activity of the parenteral form and has extremely variable and unpredictable absorption.
- Alternative analgesics with similar efficacy and less risk of adverse effects are available and should be used instead of meperidine in elderly patients.

DIPYRIDAMOLE

Dipyridamole has been used successfully as an alternative to warfarin anticoagulants to prevent thromboembolism after cardiac valve replacement. The manufacturer recommends 75 to 100 mg orally 4 times daily as an adjunct to usual warfarin therapy.

Published guidelines to alert long-term care facility surveyors to potentially inappropriate drug use state that dipyridamole is frequently a cause of orthostatic hypotension in the elderly population, and its only proven beneficial indication is in patients with artificial heart valves. Adverse effects become a major consideration when drugs such as dipyridamole are used routinely for indications for which they may not be effective.

The hemodynamic effects of oral dipyridamole were evaluated in 120 patients before thallium scintigraphy. In this series of patients, hypotension was a common but unpredictable adverse effect of oral dipyridamole. When present, hypotension tended to occur early in treatment. Hemodynamic monitoring of patients taking dipyridamole was recommended.¹⁰⁴

A recent resurgence in dipyridamole use has occurred after several controlled trials compared the use of dipyridamole alone or in combination with aspirin in preventing stroke in patients with a history of transient ischemic at-

tacks or strokes.¹⁰⁵⁻¹⁰⁷ Both aspirin and dipyridamole prevented recurrence of events in patients considered at risk, and the combination of aspirin and dipyridamole further reduced events by slightly more than one third. Examination of adverse reactions was a major end point of these studies, which included elderly patients. These adverse effects included GI intolerance, headache, and in the aspirin-treated groups, increased bleeding events. The incidences of dizziness and symptomatic hypotension were no greater than in the placebo arms of each study. Because hypotension, particularly early in treatment, appears to be a problem and the elderly population has a greater potential for complications related to hypotension, elderly patients should be monitored closely when dipyridamole treatment is initiated.

Recently published data¹⁰⁵⁻¹⁰⁷ indicate benefits from dipyridamole in certain circumstances. These data were not available when the criteria for inappropriate medications were being developed. Before this information was available, there was little evidence to indicate benefit from the drug. Although adverse effects can occur with dipyridamole use, they do not preclude its use when the drug has potential benefit. Therefore, on the basis of recently published data,¹⁰⁵⁻¹⁰⁷ dipyridamole should not be designated as an inappropriate drug when used for treatment of specific problems shown to benefit from use of the drug.

- Risks of hypotension have been associated with use of dipyridamole in elderly patients; these patients should be monitored closely.
- Although dipyridamole has been classified as an inappropriate drug for the elderly population, it benefits some individuals by preventing strokes.
- The reported adverse effects of dipyridamole should not preclude its use in elderly patients when it is prescribed for a condition for which it has been proved effective.

DIGOXIN

Digoxin is a cardiac glycoside that has been used for decades. Its use in CHF has been subjected to considerable controversy. Digoxin has 2 major actions. It exerts a positive inotropic effect, increasing cardiac output in CHF. It also has activity in the treatment of supraventricular arrhythmias due to an increase in the atrioventricular (AV) nodal refractory period. Inappropriate drug criteria raise concerns regarding the use of digoxin in higher doses (>0.125 mg/d) in the management of CHF. Higher doses may be necessary for treating atrial arrhythmias, such as atrial fibrillation.

Adverse effects of digoxin usually are related to its toxicity, which stems from its narrow therapeutic range, reportedly 0.8 to 2.0 ng/mL. Age-related changes in body mass and reduction of renal function clearly contribute to

the potential for digoxin toxicity. Renal function appears to be more important than other aging factors and affects the relationship between therapeutic dose and steady-state serum levels.¹⁰⁸ A reduced maintenance dose of digoxin is recommended when renal function is reduced with aging. A decreased loading dose is recommended when lean body mass is reduced with aging and results in a smaller volume of distribution for digoxin.

It is well known that electrolyte imbalances (hypokalemia, hypomagnesemia, and hypercalcemia) predispose patients to digitalis toxicity. Digoxin also has well-known drug-drug interactions that contribute to potential toxicity. Particularly concerning are drugs such as NSAIDs that reduce the renal clearance of digoxin.

Therapeutic drug monitoring of digoxin requires consideration of whether assays were obtained at steady state of dosing and clearance. If not, gradual accumulation may occur despite recent drug levels being within acceptable limits.¹⁰⁹ The elimination half-life of digoxin is approximately 2 days (range, 1.3-2.2 days). It takes 4 to 5 times the half-life (usually 8-10 days) before new steady-state conditions are achieved after a dose adjustment.¹¹⁰ In elderly persons, the blood level of digoxin may not always correlate with likelihood of toxicity. Many elderly persons have age-related impairment in AV nodal conduction, and some older persons show signs of AV nodal block even with relatively low blood levels of digoxin.

Adverse effects that may be recognized with early digitalis toxicity include nausea, vomiting, headache, and visual disturbances such as yellow/green vision, diplopia, blurring, and flashing lights. Typical cardiac effects seen with digitalis toxicity include partial to complete AV nodal block, junctional rhythms, ventricular extrasystoles, and ventricular tachyarrhythmias.

Several studies from 1977 to 1998 attempted to clarify the benefits of digoxin in treating CHF. Most of them were fairly small trials of New York Heart Association failure classes II and III and showed benefits of treatment or the prevention of CHF worsening. These trials measured both hemodynamic and neurohormonal effects of digoxin. Evidence suggests that digoxin may improve the neurohormonal activation at lesser doses and at higher doses may improve the hemodynamics.¹¹⁰

There is evidence to show the benefits of digoxin in therapy for CHF. Two multicenter trials concluded that continuing digoxin therapy to a serum level of 0.9 to 2.0 ng/mL was beneficial in end points of exercise tolerance and preventing worsening of CHF that required intervention. Dosages ranged higher than 0.37 mg/d, and there were extremely few problems with toxicity.^{111,112}

The Digitalis Investigation Group study was an extremely large trial from which several articles were pub-

lished about the effect of digoxin on mortality and morbidity in patients with CHF. The trial compared placebo with an average dose of digoxin of approximately 0.25 mg daily (range, 0.125-0.375 mg). Serum levels ranged from 0.5 to 2.0 ng/mL. The number of patients hospitalized with worsening CHF was significantly less in the digoxin group, but overall mortality rates between the groups were the same. Reviews of these trials concluded that digoxin improves symptoms from CHF but does not improve mortality rates, and that digoxin is a potentially useful adjunctive therapy.¹¹³ Patients with symptomatic CHF should be treated with proven beneficial treatment consisting of angiotensin-converting enzyme inhibitors, diuretics, and β -blockers. Digoxin appears to improve or prevent worsening of the failure and should be considered for patients with CHF. Prescribing a lower dose of digoxin for elderly patients, especially for those with impaired renal function, logically lessens their risk for toxicity without negatively affecting the benefits of the drug. Vigilance regarding issues of clearance and drug therapy monitoring should alert the clinician to patients who may be at risk of toxicity.

Digoxin is an option for controlling rapid ventricular response in patients with atrial flutter or atrial fibrillation.¹¹⁴ There is no evidence that digitalis by itself facilitates conversion to normal sinus rhythm. Clinicians must attempt to treat underlying predisposing factors. Digoxin may be combined with other rate-control measures. In patients with CHF and atrial fibrillation, digoxin produces favorable hemodynamic changes that may result in spontaneous conversion to normal sinus rhythm. Dosing of digoxin in this setting requires attention to avoid toxicity, especially when patients require moderately high doses or in patients with compromised renal function.¹¹⁵

Recommendations regarding the use of digoxin include limiting the dose to 0.125 mg taken once daily. This is reasonable because of the increased risks of toxicity in elderly persons primarily due to reduced renal function with aging. When higher doses are necessary, the patient should be monitored closely for signs of digitalis toxicity.

- Digoxin has been used to improve the inotropic activity of the heart in those with CHF and to treat various supraventricular arrhythmias.
- There is evidence that digitalis can prevent hospitalizations due to CHF but does not improve mortality rates.
- Toxicity from digitalis is common because of its narrow therapeutic window.
- When digoxin is used to treat CHF, doses of 0.125 mg/d are associated with lower rates of digoxin toxicity.
- In general, digoxin should be used in doses no greater than 0.125 mg/d in elderly patients. When higher doses are necessary, the patient should be monitored closely for drug toxicity.

DISOPYRAMIDE

Disopyramide is a class IA antiarrhythmic drug that has proven efficacy in the treatment of both ventricular and supraventricular arrhythmias. This drug has been labeled as inappropriate in the elderly population because of its substantial negative inotropic activity, which increases the likelihood of the drug inducing heart failure.¹¹⁶ Case series and other reports have associated the drug with substantial worsening of left ventricular function in patients with pre-existing but controlled CHF.¹¹⁷ Disopyramide also has considerable anticholinergic activity. It is no longer considered a first-line choice because of the availability of better-tolerated agents.

Disopyramide shares the potential arrhythmogenic effects of other antiarrhythmic drugs. Also, many case reports implicate it as a cause of glaucoma, urinary retention, and hypoglycemia, with potential for hepatic and renal toxicity. There are other antiarrhythmics that have compared favorably in clinical trials with disopyramide. In a double-blind, placebo-controlled, longitudinal crossover study of 27 patients with frequent ventricular premature depolarizations,¹¹⁸ moricizine showed better efficacy than disopyramide, with fewer severe adverse effects. Disopyramide has been shown to be as effective as propafenone in treating atrial fibrillation after cardioversion, but propafenone was better tolerated. Propafenone has shown greater efficacy and better tolerance than disopyramide in the suppression of symptomatic premature ventricular contractions and ventricular tachycardia.¹¹⁹

In these trials, most reported patient problems were related to the anticholinergic effects of disopyramide. Case reports and case series have shown that disopyramide also reduces fasting serum glucose levels. This occurred as a common adverse effect, even when the drug was used in normal dosage ranges.¹²⁰

The availability of other antiarrhythmic medications with fewer potential adverse effects supports the classification of disopyramide as inappropriate for elderly patients.

- Disopyramide is beneficial in the treatment of ventricular and supraventricular arrhythmias.
- Disopyramide has both anticholinergic and negative inotropic effects, which can cause considerable problems for elderly patients.

TRIMETHOBENZAMIDE

Trimethobenzamide is an antiemetic that is somewhat less effective than prochlorperazine and other antiemetics.^{121,122} This drug is considered inappropriate for elderly patients because of its lower potency and the extrapyramidal adverse effects that typically occur with phenothiazine derivatives.¹²³ Many trimethobenzamide studies occurred in the 1960s, shortly after the drug had been

released and when few other antiemetics were available. Most of these investigations did not identify adverse effects as an end point; therefore, relative safety was not statistically evaluated. There have been no studies of the propensity of trimethobenzamide to cause these problems. Some small evaluations used trimethobenzamide as a single dose and reported no additional problems; however, these studies were too small to determine the safety of trimethobenzamide.

Although few data are available, researchers have suggested that trimethobenzamide has lower efficacy than other antiemetics. Also, other available drugs have less potential for adverse effects. The literature supports the designation of trimethobenzamide as an inappropriate drug for the elderly population.

- Trimethobenzamide is an antiemetic with the potential to produce extrapyramidal effects.
- Other antiemetics are available with similar efficacy and less potential for adverse effects.

CHLORPROPAMIDE

Chlorpropamide is a long-acting sulfonylurea used to treat type 2 diabetes mellitus. It was proved effective among older sulfonylurea agents but has been replaced primarily by newer agents.¹²⁴ The inappropriateness of this drug for elderly persons is its inordinately long half-life.

Results published from the Diabetes Control and Complications Trial and United Kingdom Prospective Diabetes Study (UKPDS) encouraged intensive treatment of hyperglycemia in diabetes.^{125,126} The studies were designed to prove whether intensive hyperglycemic control reduces complications rather than prove therapy preferences among oral agents or insulin. The UKPDS treated diabetic patients with sulfonylureas including chlorpropamide, glyburide, insulin, and metformin to achieve near-normal glycosylated hemoglobin levels. Results of these trials inspired the development of newer insulin analogues such as thiazolidinediones and α -glucosidase inhibitors, which seem to compare favorably to chlorpropamide.

In the UKPDS, hypoglycemia was statistically more problematic with insulin and combination therapy; however, many cases of hypoglycemia have been linked to chlorpropamide, which clearly has a long duration of action (usual half-life of 25-42 hours and reported longer in elderly persons). Additionally, chlorpropamide has antidiuretic activity, a proven disadvantage for patients with CHF or hepatic cirrhosis. Many patients with the syndrome of inappropriate secretion of antidiuretic hormone associated with chlorpropamide have been reported and raise questions regarding hyponatremia and associated cognitive impairment. These concerns with chlorpropamide use justify the preferred use of other antihyperglycemic agents in the elderly population.

Many medications are now available with similar or greater potential benefit for diabetic patients than chlorpropamide. The long duration of action of chlorpropamide makes it a poor choice for elderly diabetic patients, and it should be considered an inappropriate drug for elderly patients.

- Chlorpropamide has an extremely long duration of action in the elderly population and has considerable potential to produce prolonged hypoglycemia.
- Alternatives to chlorpropamide provide greater safety with similar efficacy, and these drugs should be used in elderly patients.

SUMMARY

The use of inappropriate medications in elderly persons is an important issue because of the increased vulnerability of this segment of the population. There is evidence that elderly patients often are prescribed inappropriate medications and, as a result, tend to have more frequent and often serious adverse effects. The choice of medications prescribed is based on prescribers' knowledge of various pharmaceutical agents, including drugs that have increased potential for harm.

Unfortunately, cost also frequently plays a role in our selection of medications. Physicians are often bound by formularies that may limit access to the safer, but often more expensive, medications. Prescribers realize that elderly patients may not be able to afford various medications and may consider a less expensive medication with a greater potential risk of adverse effects to be better than one that patients may not take for financial reasons.

Overall, we found that the literature supports the Beers¹⁸ selection of inappropriate medications for the elderly population, although some medications had better support than others (Table 3). In many cases, elderly patients tolerate drugs identified as inappropriate without problems. In cases where safer alternatives exist, it is best to avoid drugs with considerable potential to cause problems. When a drug labeled as inappropriate for elderly persons must be used, the patient should be monitored closely while taking the drug.

Recent data suggest there has been a considerable decline in the use of inappropriate medications in elderly patients,^{127,128} possibly because many of the drugs identified by Beers et al as inappropriate are no longer used. However, serious adverse effects from medications continue to occur in elderly patients. An estimated 350,000 drug-related injuries occur annually in long-term care residents, and it is likely that more than half of these injuries may be preventable.¹²⁹ Some of these problems are caused by drugs considered inappropriate for elderly persons.

Those who prescribe medications for elderly patients face many challenges. If drug-related adverse effects in

Table 3. Recommendations Regarding Inappropriate Drugs for Elderly Patients*

Drug	Listed reasons for inappropriate status	Type of support	Reference	Comment
Anticholinergics	Cardiac arrhythmia, dry mouth and eyes, urinary retention	Case studies; controlled trials	20-23, 25	Avoid if possible
Tricyclic antidepressants	Anticholinergic, cardiac toxicity, orthostatic hypotension	Case studies; controlled trials	25, 29, 31, 32, 35	Low dose for neuropathic pain is appropriate
First- and second-generation antipsychotics	Anticholinergic effects, extrapyramidal effects, tardive dyskinesia, better alternatives available with newer medications	Case studies; controlled trials	20, 27, 42	Patients require IM or IV medication
Barbiturates	Respiratory depression, habituation, falls/hip fractures, better/safer alternatives available	Case studies; controlled trials	51, 52	Appropriate for patients with seizure disorders
Long-acting benzodiazepines	Falls/hip fractures, safer alternatives available with shorter duration	Case studies; controlled trials	55-57	Avoid if possible
Meprobamate	Respiratory depression, falls/hip fractures, tolerance, safer alternatives available	Case studies	59	Avoid if possible
First-generation antihistamines	Sedation, falls, impaired driving, safer alternatives available	Case studies; controlled trials	53, 60, 61	Avoid if possible
Pentazocine	Hallucinations, CNS impairment	Case reports; small trials were negative	83-89, 91	Avoid high doses or prolonged use
Propoxyphene	CNS impairment with associated fall risk	Case reports; small and large CRTs	92-95	More risk identified, comparative analgesic potency is weak at best
Meperidine	CNS impairment, toxic metabolite accumulation	Case reports	99-102	Oral meperidine poor, irregular absorption
Dipyridamole	Orthostatic hypotension	Case studies; case series; recent CRTs (showed lack of notable hypotension)	104	New CRTs for stroke prevention more recent than criteria
Digoxin	Daily doses >0.125 mg for CHF have more risk than benefit	CHF: small to multicenter CRTs. Atrial fibrillation: CRTs show some benefit	110-112, 117	Has benefits in CHF and atrial fibrillation. Vigilance with clearance, dosing is necessary. In atrial fibrillation there are alternatives
Disopyramide	Negative inotrope, higher risk of inducing cardiac failure. Anticholinergic adverse effects	Case reports; CRTs with other agents had fewer adverse reactions	118, 119, 122	Other agents clearly less problematic
Trimethobenzamide	Lower potency, extrapyramidal adverse effects	Case studies; case series; older randomized trials showed efficacy	123-125	Very little evidence. Other available agents may be more effective
Chlorpropamide	Overly long action, resulting hypoglycemia	Case reports; large CRTs confirm other favorable choices	126	Use other, safer alternatives

*CHF = congestive heart failure; CNS = central nervous system; CRT = controlled randomized trial; IM = intramuscular; IV = intravenous.

elderly patients are to be notably reduced, it is important not only to avoid the use of medications considered inappropriate but to use "appropriate medications" correctly. Medications should be prescribed only for appropriate reasons, discontinued when they no longer provide benefit, and dosed correctly to reflect alterations in age-related pharmacokinetics and pharmacodynamics. Finally, elderly patients should be monitored closely for drug-related problems.

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The Symposium on Geriatrics will continue in the February issue.