Pharmacologic Issues in Geriatric Emergency Medicine

Michelle P. Blanda, MD, FACEP

Department of Emergency Medicine, Northeastern Ohio Universities College of Medicine, Summa Health System, 41 Arch Street, Suite 518, Akron, OH 44304, USA

The geriatric emergency care model emphasizes older emergency patients be considered a special population, analogous to pediatric patients [1]. This concept is especially relevant to pharmacologic issues in the elderly. The need for practitioners to create a balance between using medications with adverse effects while providing access to therapies that may have a beneficial effect on morbidity, mortality, function, and quality of life is challenging. Variables affecting this challenge in the elderly population include comorbidities, limited evidence for efficacy, increased risk of adverse drug reactions, polypharmacy, and altered pharmokinetics.

Elderly patients become involved in a vicious cycle described by Rochan as the “prescribing cascade” [2,3]. This cascade begins when an adverse drug reaction is misinterpreted as a new medical condition. A drug is prescribed to treat this new “medical condition” and another adverse drug effect occurs. Again, this is interpreted as a new condition and the patient is again subjected to unnecessary treatment and additional adverse effects of the drug. Because elderly patients have multiple medical problems they are prescribed multiple medications that lead to increased risk of adverse effects. Many of these adverse effects go unrecognized as such and lead to new drugs being added. This perpetuates the continued cycle of adverse effects.

This article describes the scope of the problem of drug prescribing in the elderly. It looks at the concept of adverse drug reactions and events, principles underlying clinical geriatric pharmacology, and reviews drugs that commonly cause adverse drug reactions. It includes recommendations about drugs to be avoided and substitutes and approaches to evaluate the evidence for risk and benefits when selecting drugs for an elderly person.
Scope of the problem

Drug prescribing in the elderly is an important topic to consider because of many factors. These include the growth of the aging population, the existence of chronic illness, and the use of multiple medications. In addition, because pharmacokinetics and pharmacodynamics may be altered by age and disease, this group is at high risk to be affected. All these points increase the susceptibility for adverse drug reactions in the elderly.

In the year 2003, there were 36 million people over the age of 65 years in the United States, representing 12% of the total population [4]. This group received approximately 40% of prescribed drugs, which is twice as much as their younger counterparts [5]. It is anticipated that significant growth will occur in this age group during the years 2011 to 2030 when baby boomers, the people born between 1946 and 1964, turn 65 years old [4]. Therefore, any issues that affect this growing population will continue not only to exist but to become more pronounced.

As stated, the incidence of chronic illness and pathology increases with age, leading to polypharmacy in this group. Although the term polypharmacy carries negative connotations, use of numerous medications is sometimes necessary [6]. Despite the view that there is widespread underuse of beneficial therapies in this population, drugs with known value in decreasing mortality in clinical trials are being offered more and more to the elderly. These include mainstays of therapy such as angiotensin converting enzyme inhibitors in heart failure, antiplatelet agents in stroke, and antiplatelet agents and beta-blockers in those with myocardial infarction [7].

The elderly have more adverse drug events than any other age group because their exposure to a greater number of medications provides more opportunities for medication errors and side effects. The Sloan Survey, which was a phone survey of a random sample of the noninstitutionalized US population, reported data on the range of drugs used by the general public. For patients aged at least 65 years, this survey found that 23% of women and 19% of men took at least five medications and 12% of both women and men took >10 medications during the preceding week [5]. Others have reported similar numbers, with community-dwelling elders taking between two and six medications and one to three nonprescription medications on a routine basis [8].

The Sloan survey also reported on common vitamin and herbal use by this age group. The common vitamins used by both sexes in patients 65 years of age and older were multivitamins, vitamin E, and vitamin C. In addition, women used calcium and vitamin D. Common herbal supplements included *allium sativum*, glucosamine, and *serenoa repens* in men, and *ginkgo biloba* extract, glucosamine, and *allium sativum* in women [5] (Table 1). Awareness of the use of the full range of medications, both prescription and nonprescription, is essential for safety and to reduce risks associated with their consumption.
Adverse drug reactions

Adverse drug reactions are defined by the World Health Organization (WHO) as “any noxious, unintended, and undesired effect of a drug which occurs at doses used in humans for prophylaxis, diagnosis or therapy” [9]. This does not include therapeutic failures, poisonings (whether accidental or intentional), abuse of drugs, errors in administration, or noncompliance. Therefore, the term adverse drug reaction probably underestimates the true incidence of events related to drugs. Other terms are used instead of adverse drug reaction. “Adverse drug event” refers to any injury resulting from administration of a drug. A “drug-related problem” includes the above definitions but also includes failure to receive drugs for a medical problem and drug use without indication [10]. Most literature, however, tends not to use these broader definitions. The goal of research in adverse drug reactions is to alert physicians about the preventability of these reactions. However, one must keep in mind that literature on adverse drug reactions demonstrates that even when drugs are used properly there are still a large number of serious adverse drug reactions that occur [10].

Age-related changes affecting pharmacokinetics

Drug absorption, distribution, metabolism, excretion, and the physiologic response to drugs are altered in the elderly. The impairment of drug absorption due to resection of the gut, bacterial overgrowth, or achlorhydria is felt to have minimal clinical implications [11]. However, drug interactions can occur where one drug changes the absorption characteristics of another. The classic example of one drug binding another is the use of calcium and magnesium containing antacids. Absorption of drugs such as antibiotics, aspirin, and digoxin can be significantly impaired by concurrent administration of antacids. Drugs that change the gastrointestinal transit time may change a drug’s pharmacologic action. Practitioners should be aware and monitor patients carefully when administering these drugs.

Drug distribution may be altered significantly due to decreased lean body mass, decreased total body water, and increased proportion of body fat in

<table>
<thead>
<tr>
<th>Herb/supplement</th>
<th>Reason for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allium sativum (garlic)</td>
<td>Immune enhancing Anticancer</td>
</tr>
<tr>
<td>Glucosamine/chondroitin</td>
<td>Osteoarthritis—pain relief and prevention</td>
</tr>
<tr>
<td>Serenoa repens</td>
<td>Treatment for benign prostatic hypertrophy</td>
</tr>
<tr>
<td>Ginkgo biloba extract</td>
<td>Prevention of dementia, Alzheimers disease</td>
</tr>
<tr>
<td>Calcium</td>
<td>Osteoporosis prevention</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Osteoporosis prevention</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Prevention of Alzheimers, Parkinsons disease</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Anticancer, heart disease prevention</td>
</tr>
</tbody>
</table>

Table 1
Herbal medications and supplements used in the elderly
the aging body [12,13]. These changes in body composition lead to a decrease in the volume of distribution and an increase in the serum concentrations of drugs. Drugs that are water soluble such as coumadin, digoxin, and propanolol will have higher plasma concentrations at a given dose in the elderly. In drugs with low or narrow therapeutic windows (such as digoxin, aminoglycosides, lithium, or procainamide) this can lead to toxicity.

Serum protein, especially albumin, also decreases with age [13]. This leads to decreased binding sites for protein bound medications, higher serum concentrations, and the likelihood of more rapid clearance if normal excretion and clearance is occurring, or increased levels if not. Malnutrition is a cause of deceased serum albumin, and is common in older patients, especially those who are institutionalized. Competitive inhibition for protein binding sites by drugs can lead to displacement of one drug by another with increased levels of the drug being displaced. An example is aspirin and warfarin, where aspirin increases the unbound fraction of warfarin.

Metabolism and clearance of drugs are also changed in the elderly [12–16] (Table 2). Unfortunately, because elderly patients with comorbid conditions are excluded from many drug trials, the knowledge of drug metabolism is limited. There are age-related decreases in renal function that are not related to kidney disease. As the kidney ages there is a decrease in the glomerular filtration rate and tubular efficiency. A compensatory production of vasodilatory renal prostaglandins occurs to compensate for this decreased renal function. Drugs that impair this compensatory mechanism can cause a decrease in renally eliminated drugs. Nonsteroidal anti-inflammatory drugs are an example [17,18]. Because lean body mass decreases with age, the serum creatinine is a poor indicator of creatinine clearance, actually tending to overestimate clearance [19]. It is recommended that creatinine clearance be calculated with correction for age and weight using the Cockroft-Gault formula: (creatinine clearance = [(140 – age) × weight(kg)]/[72 × creatinine (mg/dL) × 0.85 for females]). Results of decreased renal function include

Table 2
Common drugs that have decreased clearance in the elderly

<table>
<thead>
<tr>
<th>Route of clearance</th>
<th>Drugs</th>
</tr>
</thead>
</table>
| Renal              | Cardiovascular: atenolol, digoxin, furosemide, hydrochlorothiazide, procaainamide, enalapril, lisinopril  
Antibiotics: ampicillin, ceftriaxone, gentamycin penicillin, ciprofloxacin, levofoxacin, ofloxacin  
Gastrointestinal: cimetidine, ranitidine, famotidine  
Neurologic: amantadine, lithium, pancuronium, phenobarbital  
Hepatic            | Cardiovascular: labetolol, lidocaine, prazosin, propanolol, quinidine, salicylates, warfarin  
Analgesics: acetaminophen, ibuprofen, meperidine, codeine  
Pulmonary: theophylline  
Neurologic: amitriptyline, barbiturates, phenytoin, benzodiazepines |

| Hypoglycemic drugs: chloropropamide, glyburide | |
prolonged half-life of renally cleared medications, increased serum levels, and prolonged clinical effects.

The other organ that contributes to metabolism of many drugs is the liver. Hepatic metabolism in the elderly is not only related to age, but to lifestyle, genotype, hepatic blood flow, hepatic disease, and interactions with other medications. It may be reduced up to 30% to 50% in the elderly [14–16]. Hepatic metabolism occurs through one of two biotransformation systems. Phase I reactions occur through the cytochrome P450 system, which either clears drugs or allows oxidation and activation of drugs. This occurs much more slowly in older adults. The change in Phase I reactions leads to change in the serum levels and clinical activity. Inhibitors of the P450 system cause an increase in the serum concentrations of drugs metabolized by the liver by impairing clearance of those drugs. Medications that induce the P450 system lead to decreased levels of medications metabolized by the liver. Phase II metabolism, which includes acetylation, sulfonation, conjugation, and glucuronidation, is minimally affected in the older population [14]. Cigarette smoking, alcohol use, and caffeine may also affect hepatic metabolism.

Other physiologic changes are occurring that affect the pharmacodynamics of many drugs. Age-related changes in cardiovascular function occur, and may explain the reduced compensatory capacity effect in the elderly to many drugs. Changes in cardiac morphology at a cellular level leads to decreased number of myocytes, stiffening of myocardial cells, reduced responsiveness to B-adrenergic stimulation, and clinically with decreased contractility of the heart with age. In parallel to these changes, large arteries dilate, have increased wall thickness, and increased smooth muscle tone with age [20–23]. This leads to increased systolic blood pressure and elevated left ventricular afterload, resulting in left ventricular wall thickening. This, in turn, causes decreased left ventricular compliance and impairment of diastolic function. Other changes in the older population include an increase in sympathetic outflow causing decreased sensitivity to B-adrenergic stimulation as well as autonomic and baroreceptor dysfunction leading to decreased response to posture and hypotension.

The central nervous system (CNS) is the other area where aging changes must be considered. Research now suggests that it is not a simple loss in the number of neurons that occurs with time, but subtler changes occurring at the level of synapses. Alterations in cellular Ca^{2+} capacity to deal with oxidative stress, reduced regeneration capacity (remyelination), and decrease in receptor sites as well as changes within these sites all have been identified as explanations for the diminution of CNS functioning and sensitivity to drugs in the elderly [20,24–26].

**Consequences of adverse drug reactions**

The consequences of medication-related problems are profound. Between 3% and 28% of hospital admissions can be attributed to drug-related
problems or drug toxic effects [27–29]. If fatal adverse drug reactions were classified as a distinct entity, they would rank between the fourth and sixth leading cause of death in the United States. This would rank adverse drug reactions above pneumonia and diabetes as a cause of death. This is not unique to the United States, but has also been identified in other nations’ health systems [30].

The cost of drug-related morbidity and mortality is estimated to be more than 136 billion dollars in the United States [11]. Admissions related to adverse drug reactions cost 847 million dollars in the United Kingdom, and account for 4% of hospital bed capacity [30]. Review of adverse drug reactions related to hospital admission found that 80% are directly responsible for the admission or known as “causal.” The other 20% are “coincidental,” and although not directly responsible for the admission, may have contributed to it. Almost three quarters are considered avoidable [30].

These adverse drug events are not limited to causing admissions. In hospitalized patients it is estimated that 2,216,000 patients experience an adverse drug reaction while being treated, and 106,000 of these are fatal [28]. For most hospitals this translates to about two out of every 100 admissions. These events increase the hospital cost by $4,700 dollars per admission, and if generalized to the whole US population, the cost is approximately 2 billion dollars [29].

Use of medications not documented or revealed to the physician while in the hospital is another problem. It has been described that, on average, about 1.5 additional drugs not mentioned on initial assessment of drug history, will be discovered on a second interview [31]. This has been verified by actual urine sampling of patients with analgesics, benzodiazepines, and ranitidine being reported as most commonly not disclosed [32]. This widespread phenomenon of physicians being unaware of medication used by the patient, has been described in emergency departments, surgical settings, and in office visits as well [33–35].

Drugs most commonly causing hospital admissions are listed in Box 1 [30,35,36]. Care must be exercised when reviewing this data because in the majority of studies it is difficult to say what the overall consumption of drugs is. Drugs implicated in causing adverse reactions may be more related to the frequency by which they are used. Also, no credit has been given to the benefits of the drugs. Aspirin is a classic example where there is convincing data of the long-term benefits of prophylactic use in high-risk patients [37].

Adverse drug events occur in the nursing home population as well. Rates for adverse drug reactions in nursing homes are 1.89 per 100 resident months and 0.65 per 100 resident months for potential adverse drug events [38]. For every dollar spent on drugs in nursing homes it is estimated that $1.33 in health care resources are consumed in the treatment of drug-related problems [39].

The most common drugs identified by practitioners as causing problems in nursing home residents are listed in Table 3 [38]. Warfarin is a drug that not only is identified as a problem in the hospital but in nursing homes
as well. Prescribers however, frequently do not make modifications in the warfarin dose even when drugs with well-established interactions with warfarin are prescribed [38]. Other drugs causing problems in the nursing home include psychoactive medications such as antipsychotics, antidepressants, and sedative/hypnotics. Percentages of nursing home patients using these drugs were 17%, 36%, and 24% respectively. Neuropsychiatric episodes such as oversedation, confusion, hallucinations, and delirium were the

<table>
<thead>
<tr>
<th>Box 1. Drugs implicated in Causing Hospital Admission (in order of frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Warfarin</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory agents (includes aspirin)</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Antidiabetic Agents</td>
</tr>
<tr>
<td>Cardiotonic Agents</td>
</tr>
<tr>
<td>Antiepileptic Drugs</td>
</tr>
<tr>
<td>Immunosuppressants</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
</tbody>
</table>


---

Table 3
Top 10 dangerous drug interactions seen in nursing homes

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Effect/Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin—NSAIDs</td>
<td>Increased bleeding</td>
</tr>
<tr>
<td>Warfarin—sulfonamides</td>
<td>Prolongation of warfarin’s effects due to unknown mechanism. Need to decrease dose of warfarin by 50% during and 1 week after therapy with antibiotic</td>
</tr>
<tr>
<td>Warfarin—macrolide antibiotics</td>
<td>Prolongation of warfarin’s effects due to inhibition of warfarin metabolism by macrolides</td>
</tr>
<tr>
<td>Warfarin—quinolone antibiotics</td>
<td>Prolongation of warfarin’s effects due to unknown mechanism. May be due to decrease in vitamin K production and altered warfarin metabolism</td>
</tr>
<tr>
<td>ACE inhibitors—potassium</td>
<td>Hyperkalemia can occur due to decreased aldosterone production caused by ACE inhibitors</td>
</tr>
<tr>
<td>ACE inhibitors—spironolactone</td>
<td>Both drugs increase serum potassium and can cause hyperkalemia</td>
</tr>
<tr>
<td>Digoxin—amiodarone</td>
<td>Amiodarone decreases the clearance of digoxin leading to toxicity. Decrease the dose of digoxin by 50% and monitor levels</td>
</tr>
<tr>
<td>Theophylline—quinolone antibiotics</td>
<td>Some quinolones can affect the metabolism of theophylline and lead to its toxicity</td>
</tr>
</tbody>
</table>

_Abbreviation: NSAIDs, nonsteroid anti-inflammatory drugs._

most common types of adverse drug events in this population. Falls and bleeding were half as common, and ranked as second and third.

What goes wrong? Risk factors for adverse drug reactions

Problems of drug use in the elderly range from wrong or unnecessary drugs prescribed, use of medication without appropriate monitoring, dosage too high or too low, adverse drug reactions to nonadherence, and polypharmacy. Most of the time though, adverse drug reactions are an accentuation of the drug’s known pharmacologic effect. Drugs with low therapeutic ratios (ratio between average therapeutic and toxic dose) such as cardiovascular drugs and analgesics are commonly implicated, as stated above. Also, drugs that are frequently used in the elderly are likely to be associated with adverse drug reactions. The actual effect of age alone and its relationship to adverse drug reactions has been questioned [40].

The direct relationship with the number of medications taken and adverse drug reactions is substantiated [27,41–44]. The concept of polypharmacy is challenging. It is known that several medical conditions can exist in the elderly patient. These conditions may best be treated with multiple drugs resulting in “obligatory or rational pharmacy” [45]. Toxicity of drug combinations may be synergistic and be greater than the sum of the toxicity in either agent alone. This is reflected by Col’s [27] work on adverse drug reactions related to hospital admission. It showed the odds ratio for an adverse drug reaction in those taking three to nine medications compared with those taking less than three was 1.8. The odds ratio for those taking 10 or more medications compared with those taking three or less was 13.4.

Noncompliance is another issue leading to adverse drug reactions. Patients may underuse, overuse, and misuse medications. Elderly people who live alone, use two or more medications, have no assistance in taking their medications, and who use more then two pharmacies and more than two physicians are more likely to have noncompliance [27]. Medication regimens with a greater number of pills taken per day, greater number of kinds of medications, as well as a greater number of needed medications are cited as problematic. Noncompliance is felt to be almost equally split, with half being intentional and the other half unintentional. Forgetfulness, unpleasant side effects of medications perceived as unnecessary, confusion, cost, and dislike of taking medications are all cited by patients as causes for noncompliance.

Costs of medications are also related to adverse drug reactions. This may reflect use of newer, more costly medications that may have more side effects, more drug interactions, and are prescribed by practitioners with less awareness of potential reactions in this population.

Other risk factors for adverse drug reactions in older outpatients are in Box 2. Similar risk factors are found in the nursing home population. These
include age 85 years and older, more than six active chronic medical diagnoses, low body weight or body mass index, nine or more medications, more than 12 doses of medication per day, and a previous adverse drug reaction [46,47].

Poisonings in the elderly

Data from poison control centers reveal that therapeutic errors are more common in the elderly (25% compared with 14.5% in younger patients). Elderly patients also contact poison centers more with acute or chronic conditions, especially women. This suggests that this population may not recognize the adverse drug reaction. Further prescribed drugs may be added, or self-medication may occur, complicating both the recognition and treatment of the adverse drug event [48]. Misuse of drugs also increased slightly with age, but then decreased in the oldest patients. Accidental exposures can be attributed to confusion, dementia, impaired vision, forgetfulness, or lack of knowledge or understanding of the product’s intended use. Examples of unintentional exposures are listed in Box 3.

Inappropriate medications in the elderly

Consensus criteria have been used to identify safe medication use in the elderly [49–51]. This method uses expert consensus developed through

---

**Box 2. Risk factors for adverse drug reactions in older outpatients**

- Polypharmacy (>5 medications)
- Multiple (>2) chronic medical problems
- Prior adverse drug reaction
- Dementia
- Renal Insufficiency (creatinine clearance <50 mL/min)
- Advanced age (>85 years)
- Multiple prescribers

---

**Box 3. Causes of unintentional exposures in the elderly**

- Taking extra dose of medication
- Mistaking external preparations to be given orally
- Taking nonmedicines in error
- Mistaking eye for ear drops (or vice versa)
- Mistaking another person or the pets prescription for one’s own
- Taking nonfood substances placed in food containers
literature review and questionnaire evaluation by nationally recognized ex-
perts in geriatric care, clinical pharmacology, and psychopharmacology us-
ing a modified Dephi technique for consensus building. Explicit criteria
provide useful tools for assessing the quality of prescribing and potential
risks from prescribing in the elderly. The initial criteria developed by Beers
[50,51,52] were targeted to the frail nursing home patient. Updates have
been done that are applicable to the general population of the elderly.
The published list by Beers was adopted by the Health Care Financing Ad-
ministration as a guideline for surveyors of long-term care institutions.

Medications with high severity rating for adverse reactions are in Table 4.
Some discussion of the drugs and the reasoning behind the “inappropriate”
label are discussed here. Many common themes are revealed in review of in-
appropriate drug lists. Anticholinergic drugs and drugs with anticholinergic
effects are considered inappropriate. These drugs cause mild side effects (dry
mouth, thirst, mydriasis), but can also cause toxicity with urinary retention,
agitation, hallucinations, seizures, cardiac arrhythmias, and heart block. Ther-
moregulation can be impaired, causing patients to be more at risk for heatstroke
during hot weather. Delirium and cognitive impairment can also occur.
Antiparkisonian drugs, tricyclic antidepressants (TCAs), phenothiazines, and
antihistamines are all drugs that have anticholinergic effects.

TCAs are considered inappropriate not only due to their anticholinergic
effects, but also due to their increased volume of distribution and slowed
metabolism in the elderly. Cardiac toxicity occurs more frequently in pa-
tients with cardiac disease. This may result in heart block and fatal ventric-
ular arrhythmias. Orthostatic hypotension is common. CNS effects such as
confusion and seizures are more common in the elderly. Selective serotonin
reuptake inhibitors are a better choice, although not beneficial for the treat-
ment of neuropathic pain.

Antipsychotic medications are occasionally prescribed in the elderly pa-
tient with behavioral problems associated with dementia. Antipsychotics
produce extrapyramidal and anticholinergic effects as well as tardive dyski-
nesia, which can occur after short-term and low-dose use. Newer generation
antipsychotics (resperidone, olanzapine, and quetiapine) are available with
efficacy that is similar to traditional antipsychotics but with a greater safety
record. The Food and Drug Administration recently issued a black box
warning stating that these newer antipsychotics may be associated with an
increased risk of death in the elderly, making the choice of antipsychotic
medications in elderly patients more difficult (see article on “Psychiatric
Emergencies in the Elderly Population”).

Barbiturates, except when used as anticonvulsants, are considered inap-
propriate for the elderly. This is due to their high lipid solubility and pro-
longed duration of action, which can lead to accumulation and toxicity.
Tolerance to their sedating effects occurs and disruption of rapid eye move-
ment sleep occurs, leading to unnatural sleep. Benzodiazepines are used in
anxiety mood disorders. They are categorized according to half-life and
the presence or absence of active metabolites. The older benzodiazepines (di-azepam, chlordiazepoxide, and flurazepam) have an increased volume of distribution in the elderly. This is due to their lipid solubility and increase in adipose stores that increase with age. Also, because benzodiazepines are degraded by the liver, and hepatic function changes with age, their half life can increase up to four- to fivefold in an older patient compared with a young patient [6]. Low lipid soluble benzodiazepines (lorazepam and oxazepam) have less risk for accumulation and toxicity. Use of benzodiazepines should be limited in older patients, and when used, should be used in low doses and for short-term therapy.

Traditional antihistamines are not used in the older population due to their CNS effects and their anticholinergic properties. They are present in many over-the-counter medications for insomnia, respiratory symptoms, and allergic conditions. The sedative effects decrease motor reflexes and place older patients at risk for motor vehicle accidents, falls, and hip fractures. Second-generation antihistamines are a better choice if antihistamines are felt to be of benefit to the patient.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the elderly for symptom management. NSAIDs are highly lipid soluble drugs with extensive protein binding. In the elderly there is widespread distribution of NSAIDs due to increased adipose stores. Unbound drug is also increased due to the reduction in plasma protein found in many older persons. NSAIDs are renally cleared and because there may be decreased renal function in older patients there is potential for excessive drug levels and toxicity.

Complications from NSAIDs are reported, with gastropathy being the most common [53]. These effects occur not only in the stomach, duodenum, and esophagus, but also in the small intestine and colon. Bleeding occurs, and is increased in patients taking anticoagulants and prednisone. NSAIDs may also inhibit the action of antihypertensive agents whose activity is via renal prostaglandins such as \( B \)-blockers and angiotensin converting agents. NSAIDs can also produce renal insufficiency, hyperkalemia, and fluid retention.

There is not adequate evidence to label NSAIDs as a class, as inappropriate for use in the elderly population. Beers specifically delineated indomethacin due to its CNS toxicity, and phenylbutazone because of its risk of bone marrow suppression as inappropriate. However, because NSAIDs benefit so many people, it is felt that cautious use with low doses and short-term therapy are appropriate.

Avoiding certain analgesics is recommended by the Beers guidelines. These included pentazocine, propoxyphene, and meperidine. Pentazocine is a mixed opiate agonist/antagonist with adequate efficacy but with increased risk of seizures and CNS effects compared with other analgesics. Propoxyphene is deemed inappropriate for elderly persons because of its doubtful efficacy and possibility of CNS toxicity due to the long half-life
Table 4
Inappropriate medications in the elderly

<table>
<thead>
<tr>
<th>Medication (with example)</th>
<th>Reason for status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines/anorexic agents</td>
<td>Potential for dependence, hypertension, angina, myocardial infarction</td>
</tr>
<tr>
<td>Analgesics</td>
<td></td>
</tr>
<tr>
<td>Pentazocin</td>
<td>CNS adverse effects, also mixed agonist-antagonist</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Not as effective as other narcotics</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>CNS adverse effects</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Potential for GI bleed</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Potential for GI bleed, renal failure, high blood pressure, heart failure</td>
</tr>
<tr>
<td>Antianxiety agents/sedative/hypnotics</td>
<td></td>
</tr>
<tr>
<td>Long-acting benzodiazepines</td>
<td>Highly addictive, cause more side effects than sedative/hypnotics</td>
</tr>
<tr>
<td></td>
<td>Better alternatives available</td>
</tr>
<tr>
<td>Short-acting benzodiazepines</td>
<td>Smaller doses are safer</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Highly addictive; better alternatives available</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>Highly sedating anxiolytic; need to withdraw slowly</td>
</tr>
<tr>
<td>Antiarrythmic agents</td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Negative iontrope, can cause heart failure; strong anticholinergic</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Lack of efficacy in older patients, prolong QT interval/torsades</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td></td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>May cause orthostatic hypotension</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>No better then aspirin, may be more toxic</td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline, chlordiazepoxide,</td>
<td>Anticholinergic effects (arrythmia, dry mouth and eyes, urinary retention)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxepin</td>
<td></td>
</tr>
<tr>
<td>Daily fluoxetine</td>
<td>Excessive CNS stimulation, agitation</td>
</tr>
<tr>
<td>Antispasmodics/Muscle relaxants</td>
<td></td>
</tr>
<tr>
<td>Dicyclomine, hyoscyamine, belladonna alkaloids</td>
<td>Anticholinergic effects, questionable effectiveness</td>
</tr>
<tr>
<td>carisprodop, cyclobenzaprine orphenadrine</td>
<td></td>
</tr>
<tr>
<td>Blood glucose regulators</td>
<td>Prolonged half-life leads to prolonged hypoglycemia</td>
</tr>
<tr>
<td>First-and second-generation antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Thioridazine</td>
<td>CNS adverse effects, extrapyramidal effects. Better alternatives available</td>
</tr>
<tr>
<td>Mesoridazine</td>
<td></td>
</tr>
<tr>
<td>First-generation antihistamines</td>
<td>Confusion and sedation</td>
</tr>
<tr>
<td>Diphenhydramine, hydroxine</td>
<td></td>
</tr>
<tr>
<td>Guanethidine (Ismelin)</td>
<td>May cause orthostatic hypotension</td>
</tr>
<tr>
<td>Guanadrel (Hyloral)</td>
<td>May cause orthostatic hypotension</td>
</tr>
<tr>
<td>Long-term use of laxatives (biscodyl)</td>
<td>Exacerbate bowel dysfunction</td>
</tr>
<tr>
<td>Methylidopa (Aldomet)</td>
<td>Causes bradycardia and may exacerbate depression</td>
</tr>
</tbody>
</table>

BLANDA
of its metabolite norpropoxyphene. It can also interact with warfarin and potentiate the anticoagulant effect. Meperidine is not recommended because of its poor analgesic activity when taken orally and toxicity related to the metabolite normeperidine that has a long half-life, especially in patients with impaired renal or hepatic function.

Dipyridamole had been classified as inappropriate; however, this was before there was evidence that it benefits some patients by preventing strokes. Its designation for being inappropriate for the elderly was due to hypotension seen early in therapy. However, the risk should not preclude its use if it is felt that there is potential benefit.

Preventability

Despite prescribing guidelines, inappropriate medications are still being used, and no improvement has occurred over time [54]. Improving drug benefits and limiting harm must be a goal of prescribers. The use of a large number of pharmaceuticals will always be an important component of the medical care of older patients. Resolving the tension of avoiding excessive medication use and providing access to therapies that are beneficial will only continue to be more difficult.

It is important to note that drug interactions account for one in six adverse drug reactions [54]. Therefore, regular review of prescriptions, the use of computerized prescribing, and pharmacist’s review of prescribing behavior may limit adverse drug reactions [55,56]. Factors found in patients whose adverse drug reaction contributed to a possibly preventable hospital admission included lack of documentation of serum blood levels or laboratory tests in over two thirds of cases [57]. Other preventable factors included inappropriate dose for an individual, noncompliance, and drug interactions.

<table>
<thead>
<tr>
<th>Medication (with example)</th>
<th>Reason for status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyltestosterone</td>
<td>Potential for prostatic hypertrophy and cardiac problems</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>Potential for aspiration</td>
</tr>
<tr>
<td>Nifedipine (short acting)</td>
<td>Potential for Orthostatic hypotension and CNS adverse effects</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Potential for renal impairment</td>
</tr>
<tr>
<td>Thyroid (dessicated)</td>
<td>Cardiac effects</td>
</tr>
<tr>
<td>Trimethobenzamide (Tigan)</td>
<td>Extrapyramidal side effects</td>
</tr>
</tbody>
</table>

Drugs with low severity rating are not listed. These include: cimetidine, clonidine, cyclandelate, digoxin, doxazosin, ergot myeloids, estrogens, ethacrynic acid, ferrous sulfate, isoxuprine long acting dipyridamole, propoxyphene, and reserpine.

Abbreviations: CNS, central nervous system; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

The majority of events, however, involved greater than one preventability factor.

Efforts must be made to expand the knowledge of benefits and risks in the elderly by including them in clinical trials. This is especially true for elderly patients with comorbid conditions. Without adequate research information on this population, clinicians are unable to decide whether drugs are beneficial for them and may withhold medication for fear of doing harm. The federal government has begun some programs to monitor drugs. The Food and Drug Administration’s program MedWatch collects voluntary reports on suspected adverse drugs effects in the general population but it is not adequate to develop a large database for the elderly.

The use of interdisciplinary teams to care for complex elderly patients may improve the quality of care for these patients and avoid inappropriate prescribing [58]. This has been beneficial for disease management such as congestive heart failure [59]. However, for this approach to be successful, it needs to be comprehensive and not only consider medical and pharmacologic issues, but social and financial components as well.

Another piece that is crucial in avoiding inappropriate medications is a linked information system that allows physicians to easily review and prescribe medications. This would allow physicians and pharmacists to be alerted when inappropriate medications are used, and allow easy access to alternative suggestions. These information systems should also accommodate individual status of the patient, accounting for their age-related physiologic changes and concomitant diseases.

General concepts for prescribing that are useful are based in the ethical principles of beneficence, nonmaleficence, and autonomy. Practitioners need to ask, “How will this medication benefit this particular patient”? If evidence does not exist at all or is not based in the elder population, practitioners may trial the medication and make a clinical decision if there is an overall good that has been achieved [60]. Another question that may be asked, “How will this harm this particular patient”? The high rate of adverse drug reactions should be balanced against the efficacy or uncertain efficacy in older people before a decision to prescribe is finalized. Finally, prescribers need to include the concept of what the patient wants in the decision to prescribe. Older patients may be concerned about their independence and side effects of medication rather than whether their disease or risk factors are managed according to a published guideline.

Summary

The challenge for the practitioner is to balance incomplete evidence about efficacy of medications in frail older people against the problems related to adverse drug reactions, without denying patients potentially valuable pharmacotherapeutic interventions. Prescribers need to be diligent in reviewing
medications periodically as well as when new medications are being considered. Review of updated explicit criteria is essential to understand and prescribe appropriately in this special population.

References


