REVIEW

CME CREDIT

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Avoiding adverse drug effects in elderly patients

ABSTRACT

This review delineates why commonly prescribed drugs and dosages often have unexpected responses in the elderly, and suggests ways to improve prescribing for this vulnerable population.

KEY POINTS

Drug dosages often need to be decreased because of age-related changes in weight and renal and hepatic function.

Drugs that affect the central nervous system often need to be given at lower doses to avoid patient confusion or falls.

The more medications an older person takes, the more likely he or she is to suffer an adverse drug effect.

Failure to recognize an adverse drug effect can result in misdiagnosis and the prescription of additional medications, further increasing chances for an adverse event.

Some patients stop taking a drug after experiencing side effects, because they fear the physician will discount their complaints.

CONSIDER THESE everyday situations:

- An 85-year-old man becomes anorexic and confused after taking digoxin, 0.25 mg daily, to control his rapid ventricular response to new-onset atrial fibrillation.
- A 71-year-old woman with chronic obstructive pulmonary disease develops a tremor, nausea, vomiting, and tachycardia while taking her usual dose of theophylline with the cimetidine that she bought at the grocery store to treat her dyspepsia.
- A 76-year-old man with mild renal insufficiency becomes hypertensive and is given antihypertensive medication after taking ibuprofen for 2 weeks to treat his osteoarthritis of the knee.

Although adverse drug effects such as these may occur in younger patients, they are more likely to occur in older patients, and account for 10% to 17% of the medical reasons for acute hospital admissions of elderly patients.[1]

One reason that older people have more adverse drug effects is that they take more medications. People over age 65 represent 13% of the US population, yet consume 25% to 30% of all drugs prescribed. Among community-dwelling elders, 66% of women and 50% of men take at least one prescription drug, and 5% to 10% of older adults take five or more.[2] The most common prescription drugs used by the elderly are cardiovascular, analgesic, central nervous system, and endocrine agents.

Surprisingly, nonprescription drug use has not been shown to increase with age. This situation may change, however, now that more and more drugs that were previously available by prescription only, such as ibuprofen, cimetidine, and diphenhydramine, are available

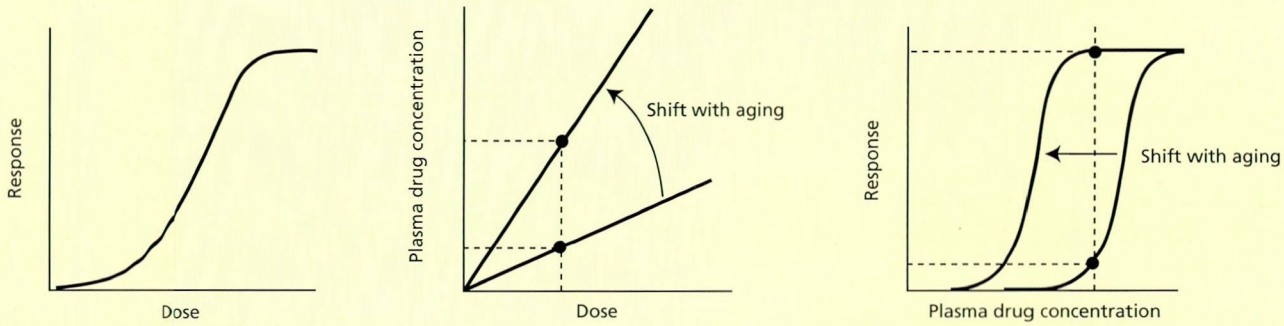

FIGURE 1. The elderly are typically more sensitive to medications due to age-related changes in the dose-response relationship.

over the counter. The most frequently consumed nonprescription drugs are analgesic and gastrointestinal products.

Appropriate medication use always requires balancing the benefits of a treatment with its risks and burdens, which are often different in the elderly than in younger patients. To maximize the benefits and minimize the risks in the elderly, physicians need to consider each patient's potential for:

- An altered dose response
- An adverse drug reaction
- Drug or disease interactions
- Difficulty adhering to the treatment regimen.

THE DOSE-RESPONSE CURVE CHANGES WITH AGING

Older adults are often more sensitive to medications, having unexpected responses to commonly used doses. This sensitivity is often due to changes in the dose-response relationship, which in turn is affected by the pharmacokinetics and the pharmacodynamics of the drug (FIGURE 1).

Pharmacokinetics describes what the body does to the drug: absorption, distribution, metabolism, and excretion. Together, these processes determine the relationship between the amount of drug given and the plasma drug concentration.

Pharmacodynamics describes what the drug does to the body: the relationship between plasma drug level and drug effect.

How aging affects pharmacokinetics

Age-related changes usually cause elderly patients to have an increased response to a given drug dose, shifting both the pharmacokinetic and the pharmacodynamic curves "to the left" (ie, they increase the plasma drug concentration at a given dose, and also increase the response to a given plasma drug concentration) (FIGURE 1).

With age, drug half-life and steady-state concentrations increase

Age-related changes in pharmacokinetics usually either prolong the drug's half-life, increasing the time it takes to reach steady-state drug concentrations, or increase the drug's concentration at steady state (due to diminished drug clearance), or both. Not only does it take longer to reach steady state, it also takes longer for the drug to be completely eliminated once stopped. Decreasing the daily dosage can counteract a decrease in drug clearance.

Clinicians prescribing for the elderly should be aware of several aspects of pharmacokinetics in healthy older persons:

Absorption. Although one would expect drug absorption to decrease with age, owing to multiple changes in the gastrointestinal tract and splanchnic blood flow, studies in fact have shown few clinically significant age-related changes in drug absorption.

Distribution. Both weight and body com-

TABLE 1

Drugs requiring dosage reduction in the elderly if renal function is diminished*

Antimicrobial drugs
- Acyclovir
- Amantadine†
- Aminoglycosides†
- Amphotericin
- Aztreonam
- Cephalosporins (cefazolin, cefepime, cefmenoxime, cefmetazole, cefonicid, cefprozil, cephalexin)†
- Imipenem
- Penicillins (most; eg, ticarcillin†)
- Quinolones (most)
- Sulbactam
- Sulfonamides
- Tetracycline†‡
- Vancomycin

Cardiovascular drugs
- ACE inhibitors (most; eg, enalapril§)
- Atenolol, nadolol, sotalol
- Digoxin
- Methyldopa
- Procainamide§

Other drugs
- Acetaminophen‡
- Albuterol
- Glyburide
- H_2 blockers (all except cimetidine†)
- Insulin
- Lithium
- Meperidine§

*All need to be adjusted for glomerular filtration rate (GFR) < 50 mL/min.
†Also need to adjust most drugs in this class for GFR 51–70 mL/min
‡Can produce azotemia (tetracycline) or increased nephrotoxicity (acetaminophen active metabolites) in patients with severely impaired kidneys
§Hepatically metabolized to active metabolites that are renally excreted

The elderly have less total body water and lean body mass, and more body fat

position change with age. Many frail elderly persons are much smaller than the average adult weight of 70 kg or more on which most drug doses are based, and small size is a risk factor for adverse drug effects.[3]

Changes in body composition also affect the initial dose needed to produce a target plasma concentration. Elderly people tend to have less total body water, lower lean body mass, and increased body fat. These changes affect the loading dose required for various drugs. For example, water-soluble drugs (eg, lithium, aminoglycosides, alcohol) should be given in lower loading doses, as should drugs that bind to skeletal muscle (eg, digoxin).

Fat-soluble drugs might, in theory, require a greater initial dose in older adults. However, in reality, many of these drugs, such as diazepam and fentanyl, are actually given in lower doses since they cross the blood-brain barrier and, for pharmacodynamic reasons, can result in adverse effects such as confusion or falls.

Hepatic metabolism varies markedly among individuals, according to age, gender, genotype, lifestyle, cardiac output, disease, and interactions with other medications. Therefore, the same dose of oral medication can sometimes result in as much as a 100-fold difference in plasma drug levels in different people.

The liver metabolizes drugs mainly through acetylation, conjugation, and oxidation. The rates of acetylation and conjugation do not change significantly with age; however, as noted above, lower doses may be appropriate for centrally acting drugs metabolized through these routes, such as lorazepam and morphine. Drugs oxidized through cytochrome P-450 isozymes, such as theophylline, felodipine, and paroxetine, are metabolized at one half to two thirds their usual rate due to age-related reductions in liver mass and hepatic blood flow.[4]

Renal excretion. In approximately two thirds of adults, the glomerular filtration rate (GFR) decreases with age, as does renal mass and blood flow.[5] The GFR correlates with the excretion of drugs primarily eliminated by the kidney and can be used to estimate initial dosing regimens. Several commonly prescribed drugs require dosage adjustments when a patient's GFR is reduced (TABLE 1).

But how to measure the GFR? The serum creatinine level alone is often misleading in older adults, as the production of creatinine declines with age, resulting in renal impairment with a normal serum creatinine level. Several formulas exist that give a "quick and dirty" estimate of the creatinine clearance

TABLE 2

Risk factors for adverse drug events in the elderly

- Altered pharmacodynamics
- Altered pharmacokinetics
- History of previous adverse drug events
- Medications with low therapeutic index
- Multiple medical disorders
- Polypharmacy
- Problems with treatment adherence

TABLE 3

Drugs that affect cytochrome P-450

Inducers

- Barbiturates
- Carbamazepine
- Chronic alcohol intake
- Cigarette smoke
- Glucocorticoids
- Phenytoin
- Rifampin

Inhibitors

- Chloroquine
- Cimetidine
- Diltiazem, nicardipine, verapamil
- Erythromycin, clarithromycin
- Fluconazole, itraconazole, ketoconazole
- Fluoxetine, paroxetine
- Methylphenidate
- Perphenazine, thioridazine
- Propafenone, quinidine
- Propoxyphene

(which is itself only a rough approximation of the true GFR and moreover requires a 12- or 24-hour urine collection). None of these is especially accurate: Malmrose et al[6] calculated the creatinine clearance using 15 different formulas in 762 community-dwelling elders, compared the results with measured creatinine clearance values, and found that the estimates varied widely from the true values.

Therefore, when considering the use of a drug listed in TABLE 1, particularly one with a low therapeutic index, drug levels and/or a 24-hour creatinine clearance should be measured. If this is not feasible, a formula such as that of Cockcroft and Gault[7] can be used as an estimate, recognizing that clinical response needs to be closely monitored. According to this formula:

$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine}}$$

When to measure the plasma drug concentration

Measuring the plasma drug concentration can detect variation in pharmacokinetics. These measurements are most useful:

- For drugs with a low therapeutic index (eg, digoxin or lithium)
- For drugs that vary substantially among individuals in dose response (eg, tricyclic antidepressants)
- When it is impossible to measure the desired effect directly (eg, anticonvulsants)
- When the patient is at high risk for an adverse event or ineffective therapy.

In older adults, toxicity may occur at a plasma level within the therapeutic range, due to pharmacodynamic considerations (see below). For example, anticholinergic delirium can be caused by "subtherapeutic" levels of tricyclic antidepressants or digoxin.

How aging affects pharmacodynamics

Pharmacodynamic differences in the elderly also can affect the response to a drug. For example, diazepam produces more sedation and memory impairment in older adults than in younger adults at the same plasma concentrations. Similarly, theophylline produces greater cardiac and central nervous system toxicity.[8,9]

Even drugs without age-related pharmacokinetic differences may require dosage adjustment. For example, to achieve the same degree of sedation, older people require lower plasma levels of fentanyl and alfentanil than do younger persons, even though the pharmacokinetics are similar for both age groups.[10]

The only known example of decreased drug sensitivity in older adults is the diminished heart-rate response to a given plasma level of isoproterenol in older adults and the greater plasma level of propranolol needed to block this isoproterenol effect.[11] Older adults may therefore be less responsive to usual doses

The elderly may have a decreased response to a beta agonist or beta-blocker

TABLE 4

Examples of drug-disease interactions in older adults

DISEASE OR CONDITION	DRUGS	EFFECT	MECHANISM
Parkinson disease, Alzheimer disease	Anticholinergics (low doses)	Confusion	Increased sensitivity
Congestive heart failure, hypertension	Nonsteroidal anti-inflammatory drugs	Precipitation or exacerbation	Sodium retention
Claudication	Beta-blockers	Precipitation or exacerbation	Unopposed vasoconstriction
Stress incontinence	Alpha$_1$ blockers	Precipitation or exacerbation	Block contraction of urethral sphincter smooth muscle
Benign prostatic hypertrophy	Alpha$_1$ agonists (decongestants) Anticholinergics Calcium channel blockers	Urinary retention	Contract prostatic and urethral smooth muscle, impair bladder contractility
Constipation	Calcium channel blockers Anticholinergics Beta-blockers Opiates	Precipitation or exacerbation, including impaction	Decrease intestinal motility and tone; often receptor-mediated

Previously well-tolerated drugs can cause new problems as patients age

of beta agonists or antagonists than some younger adults.

ADVERSE DRUG EVENTS MAY BE MISINTERPRETED

As indicated above, 10% to 17% of acute geriatric medical admissions are due to adverse drug effects,[1] defined as injuries resulting from drug-related medical interventions.

Physicians, patients, and family members may misinterpret these adverse drug effects as disorders thought to increase in prevalence in the elderly, such as falls, anorexia, and fatigue. Physicians may also misinterpret adverse drug effects in the elderly if the plasma drug level is within the therapeutic range. Another reason for missing adverse drug effects is that these differ from those uncovered during clinical trials with younger, healthier subjects.

Digoxin toxicity, for example, may present as:

- Arrhythmias with "normal" digoxin levels
- Anorexia, nausea, and vomiting
- Lethargy, depression, or confusion
- Hazy or muddy vision
- Impaired ability to perform activities of daily living.

Failure to recognize an adverse drug effect, due to a lowered index of suspicion, can result in misdiagnosis and the prescription of additional medications, further increasing chances for an adverse event.

Age alone is not generally an independent risk factor for adverse drug effects, although older adults commonly have pharmacokinetic changes that affect drug concentrations, use more medications with low therapeutic indexes, and use multiple drugs simultaneously, all of which do increase risk (TABLE 2). Many adverse drug effects are predictable responses to higher doses of the drug and could be prevented by starting at low doses and increasing dosage only after the steady state has been reached. This "start low, go slow" approach is most feasible when treating chronic, non–life-threatening conditions.

DRUG INTERACTIONS

Drugs can interact with diseases, foods, or other drugs. Many drug interactions involve induction or inhibition of cytochrome P-450

isozymes. Although each inducing or inhibiting drug does not affect *every* isozyme, drugs are often metabolized by more than one isozyme. Many drugs can affect each isozyme, so that in general it is easier to remember which drugs have been implicated in the induction or inhibition of any isozyme (TABLE 3).

Diseases affecting an organ that metabolizes or eliminates drugs, such as the liver or kidney, or the delivery of drugs to those organs, can increase the plasma concentration of the drug, and therefore the response.

Other examples of drug-disease interactions of particular concern to those caring for the elderly are noted in TABLE 4.

TREATMENT ADHERENCE

The more drugs a patient needs to take, or the more times a day that a drug needs to be taken, the poorer the compliance. Elderly patients may not adhere to their treatment if they have functional impairments, lack of motivation, or poor recall of the medication regimen. In addition, patients may not understand the drug regimen, may lack instructions on how to integrate medications after hospital discharge, or may stop taking a drug without telling the physician because a new symptom develops.

These last patients are practicing "intelligent noncompliance": they do not inform their physicians because they think the physician will discount their belief that their symptoms are due to the drug. Patients who are uncomfortable speaking honestly with their physicians may also be taking other medications, including nonprescription and alternative therapies, which can affect their health and the benefit/risk ratio of prescription medications.

Cost needs to be a major consideration when prescribing; some drugs in the same class are less expensive but just as effective.

APPROPRIATE PRESCRIBING

We may not always be able to predict a patient's risk for experiencing an adverse effect, since clinical studies often exclude elderly patients because of the presence of complicating conditions, need for multiple medications, and inability to participate in the study. The principles discussed in this paper and summarized in TABLE 5 may help minimize adverse drug effects while still treating adequately.

TABLE 5

Appropriate prescribing for older adults

- Know your patient's medications and medication history
- Individualize therapy
- Reevaluate indications for continued drug use
- Minimize dose and total number of drugs
- Start low, go slow; use blood levels judiciously
- Treat adequately; do not withhold therapy for treatable diseases
- Recognize that any new symptom may be an adverse drug effect
- Know the drugs you and your patients use
- Use new agents with caution
- Encourage treatment adherence

SOURCE: MODIFIED FROM PARKER BM, CUSACK BJ. PHARMACOLOGY AND APPROPRIATE PRESCRIBING. IN: REUBEN DB, YOSHIKAWA TT, BESDINE RW, EDITORS. GERIATRICS REVIEW SYLLABUS: A CORE CURRICULUM IN GERIATRIC MEDICINE., 3RD ED. DUBUQUE, IA: KENDALL/HUNT PUBLISHING CO. FOR THE AMERICAN GERIATRICS SOCIETY, 1996:35.

The choice of medication, dose, formulation, regimen, and the benefits and risks to be monitored should be individualized on the basis of the patient's pathophysiology, psychology, and other medications. A panel of geriatricians and clinical pharmacologists recently identified drugs that should generally be avoided in ambulatory older adults (TABLE 6).[12] This same panel also suggested limiting the doses and frequencies of certain medications and avoiding other medications in older adults with certain diseases.

Increase the dosage only after steady state is reached

By asking the patient to bring in all of his or her medication bottles on a regular basis, the physician can maintain an up-to-date list of all medications a patient takes, including nonprescription medications, supplements, and drugs prescribed by other physicians. The physician may also discover possible errors caused by confusion with generic and trade names. This exercise can also prompt the physician to identify discrepancies in record-keeping and reassess whether these medications should be continued, and if so, whether the dose level and dosing interval are still appropriate.

Studies show that many patients can tolerate stopping certain medications thought to

TABLE 6

Concerns about specific drugs in elderly patients, according to an expert panel

Antidepressants

Amitriptyline and doxepin, because of their strong anticholinergic and sedating properties, are rarely the antidepressant drugs of choice for the elderly.

Antihistamines. All nonprescription and many prescription antihistamines (eg, chlorpheniramine, diphenhydramine, hydroxyzine, cyproheptadine, promethazine, dexchlorpheniramine) have potent anticholinergic properties. Many cough and cold preparations are available without antihistamines, and these are safer substitutes in the elderly.

Diphenhydramine is potentially anticholinergic and usually should not be used as a hypnotic in the elderly. When used to treat or prevent allergic reactions, it should be used in the smallest possible dose and with great caution.

Cardiac or cerebrovascular drugs

Dipyridamole frequently causes orthostatic hypotension in the elderly. It has been proven beneficial only in patients with artificial heart valves. Whenever possible, its use in the elderly should be avoided.

Disopyramide, of all antiarrhythmic drugs, is the most potent negative inotrope and therefore may induce heart failure in the elderly. It is also strongly anticholinergic. When appropriate, other antiarrhythmic drugs should be used.

Ergot mesyloids and the cerebral vasodilators have not been shown to be effective, in the doses studied, for the treatment of dementia or any other condition.

Methyldopa may cause bradycardia and exacerbate depression in the elderly. Alternative treatments for hypertension are generally preferred.

Reserpine imposes unnecessary risk in the elderly, inducing depression, impotence, sedation, and orthostatic hypotension. Safer alternatives exist.

Ticlopidine has been shown to be no better than aspirin in preventing clotting and is considerably more toxic. Avoid in the elderly.

Diabetes drugs

Chlorpropamide has a prolonged half-life in the elderly and can cause prolonged and serious hypoglycemia. Additionally, it is the only oral hypoglycemic agent that causes the syndrome of inadequate antidiuretic hormone (SIADH). Avoid in the elderly.

Gastrointestinal drugs

Gastrointestinal antispasmodic drugs (eg, dicyclomine, hyoscyamine, propantheline, belladonna alkaloids, and clidinium-chlordiazepoxide) are highly anticholinergic and generally produce substantial toxic effects in the elderly. Additionally, their effectiveness at doses tolerated by the elderly is questionable. All these drugs are best avoided in the elderly, especially for long-term use.

Trimethobenzamide is one of the least effective antiemetic drugs, yet it can cause extrapyramidal side effects. When possible, it should be avoided in the elderly.

Muscle relaxants. Most muscle relaxants (ie, methocarbamol, carisoprodol, oxybutynin, chlorzoxazone, metaxalone, cyclobenzaprine) are poorly tolerated by the elderly, leading to anticholinergic side effects, sedation, and weakness. Additionally, their effectiveness at doses tolerated by the elderly is questionable. Whenever possible, they should not be used by the elderly.

Narcotic analgesics

Meperidine is not an effective oral analgesic and has many disadvantages compared to other narcotic drugs. Avoid in the elderly.

Pentazocine is a narcotic analgesic that causes more central nervous system side effects, including confusion and hallucinations, more commonly than other narcotic drugs. Additionally, it is a mixed agonist and antagonist. For both reasons, its use should generally be avoided in the elderly.

Propoxyphene should generally be avoided in the elderly. It offers few analgesic advantages over acetaminophen, yet has the side effects of other narcotic drugs.

Nonsteroidal anti-inflammatory drugs

Indomethacin, of all available nonsteroidal anti-inflammatory drugs, produces the most central nervous system side effects and should, therefore, be avoided in the elderly.

Phenylbutazone may produce serious hematological side effects and should not be used in elderly patients.

Sedatives

Barbiturates cause more side effects than most other sedative or hypnotic drugs in the elderly and are highly addictive. They should not be started as new therapy in the elderly except when used to control seizures.

Chlordiazepoxide and diazepam have long half-lives in the elderly (often several days), producing prolonged sedation and increasing the risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required.

Flurazepam, a benzodiazepine hypnotic, has an extremely long half-life in the elderly (often days), producing prolonged sedation and increasing the incidence of falls and fractures. Medium- or short-acting benzodiazepines are preferable.

Meprobamate is a highly addictive and sedating anxiolytic. Avoid in elderly patients. Those using meprobamate for prolonged periods may be addicted and may need to be withdrawn slowly.

Suggested maximum daily dosages for older adults

Sedatives	
Alprazolam	2 mg
Lorazepam	3 mg
Oxazepam	60 mg
Temazepam	15 mg
Triazolam	0.25 mg
Zolpidem	5 mg
Iron supplements	325 mg
Digoxin	0.125 mg

SOURCE: ADAPTED FROM BEERS MH. EXPLICIT CRITERIA FOR DETERMINING POTENTIALLY INAPPROPRIATE MEDICATION USE BY THE ELDERLY. AN UPDATE. ARCH INTERN MED 1997; 157:1531–1536

be "lifelong," such as digoxin, antihypertensives, and antipsychotics, if they are cautiously tapered from the current dose level.[13–16] Drugs that have been taken long-term and well tolerated may precipitate new conditions as patients age. Physicians need to reassess, on a regular basis, factors that can affect the pharmacokinetics and pharmacodynamics of a drug, such as renal and hepatic function, body weight, and other drugs taken, all of which can change with time.

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