

Pharmacotherapy In Geriatrics: Cause For Concern

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Pharmacotherapy in the elderly is complicated by multifactorial issues, including age-related physiologic changes, the presence of multiple chronic disease states, functional changes in neuropsychiatric and physical abilities, and the patient's desire versus ability to comply with recommended therapy. Adverse drug reactions and interactions are more common than in the general population. Geriatric clinical syndromes such as falls, fecal impaction, incontinence, etc., can be induced or exacerbated by prescribed and OTC pharmaceuticals as well as "natural" or herbal supplements. Withdrawal of pharmaceuticals may also result in significant illness.

Age-Related Physiologic Changes

Essentially all organ systems are functionally or physically altered by progressive biologic senescence associated with the passage of time. Age-related physiologic changes contribute to altered pharmacokinetics and pharmacodynamics in the older population and occur in the absence of disease. (For a detailed description of pharmacologic terms used in this article, see Villalobos et al, "Pharmacokinetics and Pharmacodynamics of Antibacterial Agents in Pediatrics," appearing elsewhere in this issue).

Enteral drug absorption in the older patient may be abnormal due to age-related changes in the gastrointestinal tract. These may include: lessened salivary flow, a smaller absorptive surface (atrophic villi), a higher gastric pH, delayed gastric emptying, reduced splanchnic blood flow and slowed gastrointestinal motility. Bioavailability may increase or decrease secondarily to alterations in absorption. The consequence may be either drug toxicity or disease undertreatment at standardized dose or dose interval recommendations (see Table 1).

Altered distribution of a drug is determined in large part by body weight and composition, plasma protein binding, and in a few cases, by red blood cell binding. Lean body mass decreases over time, as fat content increases, resulting in a 25% to 45% increase in the body fat to body weight ratio. Lipophilic drugs may have prolonged half-lives as the body fat to lean body mass ratio increases, resulting in accumulation of a drug to toxic levels. In females, this ratio may be even higher, accounting at times for increased sensitivity to lipophilic drugs. Large decreases in total body water, particularly extracellular fluid, may occur.

As the volume of distribution of a polar, water-soluble drug decreases, drug half-life increases. The predominant plasma binding proteins are albumin, which may be slightly decreased in the healthy elderly, and alpha-1-acid glycoprotein is slightly increased. Levels of both vary significantly in the older adult. Alterations in protein binding influence the concentration of free drug moiety available in the circulation. Decreased levels of albumin, common in the frail elderly, may lead to drug toxicity due to lower availability of binding sites. Increased levels of alpha-1-acid glycoprotein,

particularly due to its role as an acute phase reactant, may lead to lower levels of unbound, active drug in the circulation (Table 1).

Table 1. Factors affecting pharmaco-physiological responses in the healthy elderly		
<i>Physiologic Parameter</i>	<i>Histophysiological change with age</i>	<i>Significance</i>
Absorption	Decreased salivary flow Increased gastric pH Delayed gastric emptying Decreased absorptive surface Reduced splanchnic blood flow Decreased gastrointestinal motility	Mildly decreased absorption
Distribution	Decreased lean body mass Increased body fat:lean body mass ratio Decreased total body water Decreased serum albumin Increased alpha-1 acid glycoprotein	Increased distribution and t-1/2 of lipophilic drugs Higher concentration of polar, water soluble drugs Increased free fraction in plasma of protein-bound acidic drugs Decreased free fraction of basic drugs
Metabolism	Decreased hepatic metabolic capacity Decreased hepatic mass Decreased hepatic blood flow	Decreased Phase I biotransformation (oxidation / reduction, hydrolysis) Decreased first pass-metabolism
Elimination	Decreased renal blood flow Decreased glomerular filtration rate	Decreased elimination of drugs and metabolites

Drug clearance by Phase I hepatic metabolism (oxidation, reduction, hydrolysis) is more likely than Phase II (conjugation) to be impaired with aging. It is well known that liver function, as measured by biochemical parameters as well as by microsomal and cytoplasmic enzyme activity, does not tend to decline significantly with age. What does change, however, is the metabolic capacity of the liver, because both liver mass and blood flow decrease about 40%, probably due to a decline in the percentage of cardiac output received. Some common environmental factors (e.g., tobacco, alcohol, caffeine, polypharmacy and acute illness) may influence metabolism more significantly than age alone.

Clearance by elimination via altered renal structure and physiology in the elderly frequently is responsible for altered drug levels. Even in healthy adults, renal function declines steadily with age as a result of decreased renal blood flow, loss of cortical mass, a resultant progressive reduction of glomerular filtration rate, and reduced tubular secretion. (See Table 1). Clinically, measurement of renal function can be done most accurately with a 24-hour urine collection for creatinine clearance. Although the various creatinine clearance estimates made by calculation of equations are convenient, they frequently are inaccurate in the elderly; serum creatinine levels may appear normal or low due to an age-related decline in creatinine production and loss of lean body mass. This is deceptive and should not be overlooked when determining appropriate doses of medications. Drugs with a narrow therapeutic index should have trough and peak blood levels drawn after three to five half-lives of dosing, because bioavailability and other clearance mechanisms may alter dosing requirements that were determined by estimates of creatinine clearance. Dosage adjustments for renal impairment are required for aminoglyco-sides, digoxin, lithium, pro-cainamide, and theophylline.

Pharmacodynamics in the older adult, (i.e., the action of a drug on the body at the level of cellular, subcellular and nuclear receptors), is more complicated and certainly less predictable. Not only can the number of target receptors change with cellular aging, but the sensitivity and/or specificity of the receptor itself may be altered. For instance, the efficacy of beta-blockers diminishes with age, more likely due to reduced sensitivity of the beta-receptor than due to down-regulation of receptors. The elderly, however, seem to have increased tissue sensitivity to drugs targeting the CNS. Because we know little at present about receptor alterations in the elderly, we can only postulate that some of the idiosyncratic, exaggerated reactions or poor responses to medications may be attributable to these receptor modifications. We have learned more, however, about the additive and opposing pharmacodynamic effects of some drugs used in combination. Combinations of two or more drugs with similar actions can have additive effects: increased CNS depression can occur with combinations of hypnotics, benzodiazepines and/or narcotics; a combination of antihistamines, tricyclic antidepressants and/or antipsychotics may have dramatically increased anticholinergic side effects. In addition, if two or more drugs are administered that act at opposing receptor sites, the action of the medications can be neutralized: a combination of an alpha-2 adrenergic vasoconstrictor and a beta-2 adrenergic vasodilator may cancel out any effects on peripheral vascular resistance (Table 2).

Table 2. Drugs commonly associated with adverse side effects in the elderly		
<i>Drug Class</i>	<i>Specific Drugs</i>	<i>Undesirable Effects</i>
Anticholinergics	Antidepressants	Exacerbation of bladder outlet obstruction (e.g. BPH); Delirium superimposed on dementia; Exacerbation of dementia; Impaired cognitive function in the non-demented; Agitation / Anxiety; Sedation; Constipation; Postural hypotension / falls; Tachycardia & decreased myocardial contractility in the patient with CHF / angina
	Antihistamines (often OTC combinations)	Delirium; Dry mouth (may lead to excessive water intake in patients with CHF); Sedation; Constipation; Glaucoma exacerbation; BPH exacerbation; Reflux esophagitis
	Antipsychotics	Overflow incontinence exacerbation; Sedation; Immobility; Falls
Dopamine-blockers	Antipsychotics Metoclopramide Prochlorperazine	Gait / balance disorders / Extrapyramidal effects Postural instability; Falls; Delirium Postural instability; Falls; Decline in function
Diuretics	HCTZ HCTZ, furosemide, spironolactone	Decreased glucose tolerance in the diabetic Increased risk of dehydration / electrolyte abnormality
Sedative / Hypnotics	Benzodiazepines Chloral hydrate Diphenhydramine	Delirium; sedation; balance instability Exacerbation of dementia Delirium; confusion; urinary incontinence, postural instability / falls

Multiple Medical Problems

The older adult often tolerates the presence of two or more chronic disease states, many of which are progressive in nature. As most disease has effects on more than one body system, interdependent physiologic reserves are further compromised. When an acute problem occurs, whether related or not to the chronic diseases, the patient decompensates. The consequence may be as simple as a visit to the doctor's office. However, results often include hospitalization or a decline in function that is not overcome with rehabilitation or long-term nursing care. Death is the ultimate decompensation.

The issue, for the purposes of this discussion, is understanding that our pharmaceutical manipulations inadvertently may cause devastating consequences to our elderly patients. Homeostatic changes encountered during normal aging may alter sensitivity to a given medication, resulting in pharmacodynamic effects. Such effects may differ markedly from reactions seen in younger patients. Multiple drugs, drug side effects, drug interactions, and drug-disease interactions contribute to the risks assumed when treating the elderly patient. Common pharmacodynamic reactions in older patients include agitation, falls, confusion, constipation, incontinence, memory deficits, dizziness, and depression. If not appropriately treated as an iatrogenic pseudodementia or delirium, the patient may be labeled with an unwarranted diagnosis and the offending drug(s) continued. Adverse drug withdrawal events may further complicate the clinical outcome. Commonly, drug withdrawal events may occur with digoxin, furosemide and psychotropic medications.

Drug-disease interactions are not uncommon. Distribution of a drug may be impaired by congestive heart failure; bioavailability of a protein-bound drug may be enhanced to the point of toxicity in malnourished, hypoalbuminemic patients; drug half-life may be increased dramatically by chronic liver disease or advanced renal insufficiency. Ventricular arrhythmias may occur in patients with ischemic heart disease who are receiving tricyclic antidepressants or phenothiazines. Orthostatic hypotension may be induced by many medications, including diuretics, alpha-adrenergic blockers, nitroglycerin preparations, phenothiazines, diphenhydramine, antipsychotics and antidepressants (Table 2).

Polypharmacy And Adverse Effects

With multiple disease processes come multiple pharmaceutical interventions. In the United States, people 65 and older account for 30% of prescription drug use (and 40% of OTC medications). Two or more drugs are prescribed to 44% of patients older than 75 years. These may enhance the older adult's well-being and general health, improving function and increasing longevity. On the other hand, as the number of medications prescribed increases, we see increased rates of adverse drug reactions, drug-drug/ drug-disease/ drug-nutrient interactions, and frequently prohibitive costs leading to non-compliance. Drug reactions or interactions account for approximately 5% of hospital admissions in the elderly, e.g., gastrointestinal bleeding from NSAIDs, falls with injury from psychotropics. One study of 293 admissions over a one-year period noted that 10% were primarily drug related. It is estimated that adverse drug effects occur during hospitalization in 25% of older patients. Incidence is a direct correlation with the number of drugs prescribed. Using fewer drugs in lower doses should decrease the risk of adverse reactions/interactions but improve compliance.

Resisting the temptation to treat every symptom with a medication is important. For instance, insomnia can be addressed through a variety of methods, including evening back rubs, soft music, a cup of warm milk, etc. Resorting to sedation with diphenhydramine or benzodiazepines should be avoided if at all possible. CNS side-effects as well as falls are common in elderly patients using these medications.

Also of concern is the healthy elderly person who self-medicates with over-the-counter medications. When a healthy older patient presents for a routine exam, one should inquire about what vitamins, herbs or other OTC medications he/she may be using at home, for what purpose, and with what frequency. This will provide an opportunity to instruct the patient in appropriate usage and of the risks involved if any. Analgesics, antihistamine/decongestant combinations, laxatives, and fad diet items may ultimately cause significant illness; if the patient is also taking prescribed medications, the risk of drug interactions increases. For instance, a patient taking theophylline for COPD decides to purchase cimetidine over-the-counter for his indigestion. The combination can lead to nausea/vomiting, cardiac arrhythmias, and seizures consistent with theophylline toxicity secondary to inhibition of drug metabolism.

It is common to see a 74 year-old patient with hypertension, insulin-requiring type II diabetes, hypercholesterolemia, COPD due to on-going tobacco dependence, degenerative joint disease and osteopenia. This patient may present to the emergency department with hip fracture secondary to falling during a brief "dizzy spell." The hospital course will likely be a complicated one; by the time the patient is stable for discharge to nursing home or rehabilitation center, he/she may be receiving additional treatment for congestive heart failure, deep venous thrombosis and pneumonia. Prior to the fall, this person may well have been independent, socially interactive, competent to make and keep his/her doctors' appointments and to drive to the library, grocery or church. One "dizzy spell" has thus led to total dependence, incontinence of bladder, a marked increase in the number of medications to be consumed, inability to walk unassisted (much less drive), profound generalized weakness, isolation from friends and activities that brought pleasure, and loss of self-esteem. Disorientation and delirium treated with antipsychotics (causing extrapyramidal side effects) may compound problems with rehabilitation, as will unrecognized depression. It is unlikely that this patient will ever return to his/her prior level of independence.

Pearls

1. Start low, go slow. Start psychotropics at $\frac{1}{2}$ to $\frac{1}{4}$ of the "recommended" starting dose.
2. Avoid drugs with a prolonged half-life when possible. Oxazepam is the preferred benzodiazepine in older patients.
3. Review both prescribed and OTC medications/ vitamins/ herbs with the patient on each visit.
4. Give the patient and/or the family a written list of medications, the purpose of the drug, dosing intervals and potential side effects. Strive for once or twice a day dosing.
5. Make sure that for every medication taken (prescribed or OTC) there is an indication.
6. Encourage the patient (or family) to report problems with compliance, (e.g. medication expense, personal fears of taking drugs, symptoms that may be side effects of the medications).

7. Consider the use of anticonvulsants (e.g., valproate sodium) instead of antipsychotics in dementia patients with overtly aggressive behavior.
8. Try to tailor a drug's known side effects to a patient's needs; for instance, trazodone may be the ideal selection for a patient with hypertension, insomnia/anxiety, depression and chronic pain or neuropathy.
9. When a patient has new complaints, remember that drugs can cause illness.

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Jacksonville Medicine / August, 1998