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The Rational Use of Drugs in the Elderly

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Editor's Note—*"The doctor of the future will not give medicine, but will interest his patient in the care of the human frame, in diet and in the cause and prevention of disease."—Thomas Edison.*

Obviously, this prediction from the most prolific inventor in American history has not come true. More than 90% of the elderly take some form of medication on a regular basis. Nursing home patients take an average of 7-8 medications per day.[1] Hospitalized Medicare patients receive an average of 10 different prescription drugs. Adverse drug reactions lead to a significant percentage of hospitalizations. For the first time, the cost of prescription drugs is now exceeding the cost of hospitalization for patients in the United States. The escalating cost of prescription drugs is largely responsible for the double-digit inflation in healthcare premiums that are being seen in many parts of the country this year. Primary care physicians (PCPs) are at the front line of this battle between cost and quality. The debate over prescription drug coverage by Medicare was one of the polarizing features of our recent presidential election. Obviously, the advances in the pharmaceutical industry have led to revolutionary improvements in the treatment and cure of a host of diseases. However, in the context of an aging population, appropriate prescribing by PCPs will be a principal determinate of how Americans attain high-quality, cost-effective medical care. This issue reviews the elements of pharmacokinetics and pharmacodynamics in the geriatric patient and outlines methods to reduce the risk of adverse drug reactions and polypharmacy in this high-risk population.

Scope of the Problem

"...even when the correct diagnosis is made, the aged are frequently improperly treated through our ignorance of the action of drug(s) upon the senile organism…Ask yourself if you have any other rule for diminishing dose in old age than a rough guess."—IL Nascher, 1912.

Although the elderly comprise about 12% of the population, they represent use of approximately 35% of all prescription drugs, 34% of all days in short-stay hospitals, and comprise 87% of all residents in nursing homes. The average elderly patient takes 4.5 prescription drugs and 3.5 over-the-counter (OTC) drugs each day and 13 different prescription medications per year.[2] Prescription drugs are the largest out-of-pocket expenses for three-fourths of the elderly, and up to 15% of the elderly are unable to pay for their medications. Although Medicare pays for the majority of the costs of hospitalizations, diagnostic testing, and physician bills, it does not cover the cost of outpatient prescription medications. The recent partisan debates in Congress are no longer arguing over whether such coverage is needed, but how to pay for it. Pharmaceutical costs are expected to rise 15-18% per year over the next five years. Total prescription drug expenditures are

expected to rise 15-18% per year from 2000 to 2005 to a total of more than $212 billion.[3]

The exploding growth in alternative medicine and OTC drug use is especially prevalent in the elderly. Nearly 40% of those older than the age of 60 use OTC preparations daily or seven times the rate of younger adults.[4]

Intelligent prescribing by PCPs is even more urgent today considering the increasing cost of this component of our health care system. The costs of prescription drugs are competing for adequate reimbursements to hospitals, physicians, and other needed medical interventions. Seventy-five percent of office visits to general practitioners and internists are associated with the continuation or initiation of a prescribed medication. Thirty-five percent of office visits by those older than 85 years result in the prescribing of three or more medications.[5] With increasing drug usage comes the risk of adverse drug reactions. It is estimated that 1.5 million persons are hospitalized annually due to adverse drug reactions.

Pharmacologic Principles

"All substances are poisonous, there is none which is not a poison, the right dose differentiates a poison from a remedy."—Paracelsus, circa 1538.

Whenever a drug is administered to a patient, its concentration depends upon its rate and extent of absorption, tissue distribution, rate and extent of drug metabolism, and excretion. Pharmacokinetics deal with the influence of these various factors in getting the drug to the specific site of action. Pharmacodynamics deal with the effect of the drug on the organism at the receptor site. The geriatric hypothesis states that the elderly are more susceptible to adverse drug events due to age-related alterations in pharmacokinetic and pharmacodynamic processes.

Pharmacokinetics Pharmacodynamics

Drug ⇒ specific site of action = receptor ⇒ action

Drugs are eliminated through two basic kinetic mechanisms. *First-order kinetics* identifies a mathematically predictable concept that can be reliably used by practitioners in predicting drug concentration and effect. Drugs are eliminated through first-order kinetics, which can be defined by the following formulas:

t½ = 0.693/K Vd/clearance

t½ = apparent half-life of drug elimination during terminal phase of plasma concentration curve after distribution equilibrium has been obtained

Vd = Volume of Distribution = a hypothetical volume relating to amount of drug in body to plasma concentration at all times after attainment of distribution equilibrium, not a physiologic parameter

Vd = total dose in body/concentration in plasma

Peak concentration after loading dose = dose (mg/kg)/Vd (L/kg)

Vd × (C) = amount of drug in body (represent proportionality constant); indication of extent of drug distribution outside of vascular region

Clearance = dose/AUC (area under curve = plasma concentration × t)

Loading dose = Vd × IBW × desired plasma concentration

Although most drugs are metabolized through first-order kinetics, a significant number of important and commonly used drugs are metabolized by *zero-order kinetics* (a dose-dependent, capacity limited, and saturable elimination process). Drugs metabolized through zero-order kinetics have the following characteristics: the half-life increases with increasing drug dose and increasing drug doses result in a nonlinear disproportionate increase in drug concentration and pharmacologic response. Common examples of drugs metabolized through this pathway are ethanol, salicylates, phenytoin, and theophylline. One rule-of-thumb is that if there exists a commercially available drug level, that drug is either metabolized through zero-order kinetics or has a narrow therapeutic window.

One common mistake in doing blood levels is that practitioners perform them too often and too soon. The time to reach steady state requires approximately five half-lives. Unless there is evidence for toxicity or inadequate therapeutic response, the physician should be patient and wait for the passage of five half-lives before performing drug levels to adjust dosage.

Pharmacokinetics

"No families take so little medicine as those of the doctors, except those of apothecaries."—Oliver Wendell Homes, 1860.

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Pharmacokinetics are those processes that influence the delivery of a drug to the site of action. Those processes include drug absorption, distribution, metabolism, and excretion. There are many reasons why these processes are altered in the elderly due to age-related changes.

Drug absorption would be expected to be irregular and unpredictable in the elderly. With aging, there is decreased stomach acidity that causes certain weakly acidic drugs to become more ionized and, therefore, less readily absorbed. Hypochlorhydria and acholorhydria are 10 times more frequent in the elderly leading to decreased absorption of calcium and weakly acidic drugs such as barbiturates. Gastrointestinal motility is reduced, intestinal blood flow is slowed, and active transport is diminished with decrease in absorption of iron, thiamine, calcium salts, and vitamin A. Because the elderly more commonly use antacids, absorption of digoxin, cimetidine, tetracycline, and propranolol may be decreased. On the other hand, increased use of laxatives in the elderly may reduce the quantity of drugs that are absorbed. Despite these theoretical reasons as to why the elderly should have irregular and unpredictable absorption, there is little good evidence that drug absorption is significantly impaired in the elderly since most drugs are absorbed passively and are not affected by many of the factors addressed above.

Drug distribution as related to volume of distribution is significantly altered. With aging, total body water decreases absolutely—as a percentage of body weight.[2] Lean body mass declines 25-30%. Body fat and its percentage of total body weight increase through middle age and then body fat content tends to decrease after the age of 65-70. For highly lipophilic agents such as benzodiazepines, increased body fat in the elderly resulting in increased volume of distribution combined with slower hepatic extraction can lead to markedly increased half-lives with a prolonged pharmacologic effect. For water-soluble drugs (such as aminoglycosides, acetaminophen, and alcohol), the decreased volume of distribution can lead to exaggerated biological effects.

As hepatic function and nutrition decline in the elderly, decreases in plasma protein levels are not uncommon resulting in decreased drug binding and increased free drug level with enhanced pharmacologic effect. Particular care should be exercised in drugs that are highly protein bound such as phenytoin, furosemide, warfarin, tolazamide, and other sulfonylureas.

In the very elderly patient, body weight tends to decline and drug dosage should be modified based on age and weight, not unlike what is commonly done for pediatric patients. Because most drugs come in dosage strengths targeted and studied in middle-aged patients, physicians should be aware of age-related changes in body weight and dose accordingly. An interesting study by Campion showed that practitioners commonly overdose lower weight patients on a milligram-per-kilogram basis.[6] Even pharmaceutical manufacturers often fail to provide dosage flexibility. As Cohen opined, no one would expect Shaquille O'Neal or a 96-year-old grandmother to take the same dose, but that's how one of the best selling drugs of all time, loratadine (Claritin®), comes—only in 10 mg tablets.[7] However, if more precise dosing is required, it is now available in syrup at a concentration of 1 mg/mL.

The use of warfarin is always fraught with danger, but especially in the elderly. The interaction with acetaminophen (which was thought to be safe to use up until 1988) has now been well documented.[8] Dosing of warfarin has been the subject of many studies but with little consensus. Obviously, the best way to dose warfarin is by closely monitoring the international normalized ratio (INR) and by paying close attention to the patient's diet and nutritional status. The following formula attempts to estimate the patient's maintenance dose and takes into account the patient's age and body weight.[9]

Maintenance dose of warfarin =
4 mg + (0.05 × weight [kg] - (0.06 × age [yr])

Drug metabolism is clearly reduced in the elderly. Liver size decreases with age, both absolute and relative to total body weight. Hepatic blood flow decreases 40% from age 25 to 75. The drug metabolizing microsomal enzyme system acts on a broad spectrum of exogenous substances (e.g., insecticides, food additives, pollutants, and chemical carcinogens). There are two major types of liver metabolism. The first, phase I (commonly referred to as nonsynthetic or preparative reactions), involves the microsomal cytochrome P450 enzymes. These enzymes are most prominent in the liver but can be found in many other organs. These enzymes are identified by the letters 'CYP' followed by an Arabic numeral, a letter, and another Arabic numeral (e.g., CYP2D6).[10] This microsomal enzyme system promotes metabolism through hydroxylation (e.g., phenobarbital), n-dealkylation (e.g., methamphetamine), oxidation, o-dealkylation, deamination, N-oxidation, desulfuration or sulfoxidation (e.g., phenothiazine).[11] These reactions generally produce relatively minor molecular modifications yielding more polar, water-soluble molecules with much of the parent drug's pharmacologic activity. This system is more consistently impaired with aging and is impaired more in men than in women.

The second type of metabolism, phase II or synthetic biotransformation, usually involves drug substrates that contain hydroxyl, amine, or carboxylic groups. Phase II processes result in the conjugation (most commonly with glucuronic acid—also involving methylation and acetylation) of these groups, thereby producing a larger compound that is highly water-soluble, pharmacologically inactive, and renally excreted. For the most part, phase II processes are not significantly impaired in the elderly. Some drugs (notably phenytoin, digoxin, propranolol, and imipramine) are metabolized through both mechanisms. Chronic alcohol ingestion and cigarette smoking (with variable use in the elderly compared to younger groups) induce enzymes in both phase I and phase II. The *Physicians' Desk Reference* (although not always detailing a drug's specific metabolic pathway) is useful if it indicates that the chemical composition of the drug contains a hydroxyl, amine, or carboxylic group. If so, the likelihood is that the drug is metabolized through conjugation phase II processes, which are not impaired with aging.

The pharmacologic effect is not always terminated by metabolism. In fact, codeine is metabolized by CYP2D6 to morphine, which is a more powerful analgesic metabolite, and

this transformation accounts partially for its clinical effect.[10] Approximately 7-10% of Caucasians have a genetic deficiency in the enzymatic expression of CYP2D6 and are designated as poor metabolizers. Therefore, these patients may not receive the full analgesic effect of codeine even from increasing doses. Asians and African-Americans are less likely than Caucasians to experience this genetic polymorphism.

In contrast, due to increased volume of distribution and reduced hepatic clearance, diazepam's half-life increases markedly in the elderly. Preferable benzodiazepines to use in the elderly would be lorazepam and oxazapam because they are not metabolized by the hepatic mixed function oxidase system but rather by glucoronidation.

The cytochrome P450 system is responsible for the majority of hepatic phase I metabolic processes. These enzymes can be induced (i.e., activity enhanced) by certain pharmacologic agents such as cigarette smoking, phenytoin, and chronic alcohol ingestion. Such enzymatic inducement shortens the half-life of drug substrates that are metabolized through this pathway and reduces the duration of their clinical effects. Other agents serve either as direct inhibitors or as competitive substrates for the P450 cytochrome system leading to extended half-lives and a prolonged clinical effect. A short list of common inhibiting and inducing agents can be found in Table 1.

In regard to drug excretion, kidney function in the elderly becomes progressively impaired both from the aging process and from the presence of common comorbid diseases such as hypertension, diabetes, and atherosclerosis. Serum creatinine is not a sensitive index of declining renal function in the elderly, as it may remain constant due to decreased lean body mass and decreased creatinine production. Therefore, even a small rise in serum creatinine may indicate significant reduction in renal function. Examples of drugs renally excreted are cimetidine, digoxin, lithium, chorpromamide, procainamide, and most of the commonly used antimicrobials such as penicillin, cephalosporins, fluoroquinolones, and aminoglycosides. The most often used technique to estimate renal function uses the Cockroft-Gault formula. This formula provides an acceptable estimate of creatinine clearance in adults except when the serum creatinine is changing rapidly or when the patient is markedly emaciated.[12]

Cockroft-Gault formula for estimating renal function:

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

For women: multiply answer by 0.85

Pharmacodynamics

"He's the best physician that knows the worthlessness of the most medicines."—Benjamin Franklin, 1733.

The pharmacodynamic hypothesis is that the observed drug sensitivities in the elderly result from changes in the quality and quantity of drug receptor sites. Certain drugs display an

Table 1. Common Microsomial Enzyme Substrates, Inhibitors, and Inducers[10]

	Substrates	Inhibitors	Inducers
CYP2D6	Antidepressants Antipsychotics Beta-blockers Narcotics (codeine, tramadol)	Paroxetine Cimetidine Fluphenazine Haloperidol	
CYP3A	Alprazolam Triazolam Calcium channel blockers Glyburide Lovastatin Sertraline Theophylline Protease inhibitors	Antidepressants (nefazodone, fluvoxamine, fluoxetine, and sertraline) Ketoconazole Cimetidine Diltiazem Erythromycin	Carbamezepine Phenobarbital Phenytoin Rifampin
CYP1A2	Amitripyline Imipramine R-warfarin Theophylline Tacrine	Fluvoxavine Grapefruit juice Quinolones	Omeprazole Phenobarbital Phenyltoin Smoking Charcoal-broiled meat
CYP2E1	Acetaminophen Ethanol	Disulfiram	Ethanol Isoniazid
CYP2C9	NSAIDs Phenytoin S-warfarin Torsemide	Fluconazole Metronidazole Itraconazole Ritonavir	Rifampin
CYP2C19	Diazepam Imipramine Omeprazole Propranolol	Fluoxetine Sertraline Omeprazole Ritonavir	

increased sensitivity or more profound effect in the elderly compared to young adults, even when serum drug concentrations are comparable. Examples of such drugs with increased effect include warfarin, benzodiazepines, halothane, metoclopramide, fentanyl, alfentanil, and narcotic analgesics. Other agents in the elderly display decreased sensitivity, such as the cardiac effects of isoproterenol and propranolol.

Chronotherapy is a recently recognized feature of prescribing principles that works in conjunction with pharmacokinetics and pharmacodynamics.[13] The body's circadian rhythm produces temporal patterns of disease and symptom manifestations and may suggest more appropriate timing of pharmaceutical interventions. It is well known that heart attacks occur more frequently in the early morning. Hay fever symptoms peak upon awakening. Migraine patients tends to awaken with headaches. Blood pressure is higher in the late afternoon or early evening. A controlled-onset extended-release verapamil (Covera-HS®) is the first chronotherapy of hypertension and angina. HMG-CoA reductase inhibitors are more effective if administered in the evening in order to coincide with the peak enzyme activity for cholesterol synthesis. An exception is atorvastatin (Lipitor®), which can be given morning or evening due to its long half-life and active metabolites.

Identifying and Reducing Adverse Drug Reactions

"Poisons and medicine are oftentimes the same substance given with different intents."—Peter Mere Latham, 1836.

The elderly are more likely to have adverse drug reactions (ADRs) and more likely to express atypical reactions to drugs. Additionally, unfavorable or undesirable drug responses are less easily recognized in the elderly. An ADR, as defined by the World Health Organization, is any noxious unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy.[14] The definition excludes therapeutic failures, poisonings, and drug abuse. ADRs that cause fatigue, listlessness, and poor memory would easily be identified in young adults but might be simply attributed to "old age" in the geriatric patient. An example would be digoxin, which can cause anorexia and mental confusion even within therapeutic levels.

ADRs may be responsible for up to 140,000 deaths each year in the United States. The cost of such drug-related morbidity and mortality is estimated to exceed $136 billion a year.[15] Fatal ADRs occur in 0.32% of hospitalized patients, ranking ADRs between the fourth and sixth leading cause of death in the United States.[14] The recent Institute of Medicine's report on drug errors, *To Err is Human*, takes into consideration some of the ADRs that are identifiable and largely predictable and preventable.[16] A study of 4108 hospitalized adults revealed the rate of adverse drug events to be six per 100 admissions and 26% of those were considered to have been preventable.[17] Compared to younger patients, the elderly are three times more likely to have ADRs in the hospital and four times as likely in the outpatient setting.[4] Clinical drug-drug interactions occur in 3-5% of patients taking a few medications, but the rate increases to 20% in patients receiving 10-20 drugs.[18] Table 2 summarizes some of the physiological changes in the elderly that predispose them to ADRs.

Table 2. Physiologic Changes in the Elderly that Predispose to Adverse Drug Reactions

Body composition

- Increased fat
- Decreased skeletal muscle mass

Hepatic function

- Decreased blood flow
- Decreased liver mass
- Decreased synthesis of albumin
- Impaired phase I drug metabolism

Renal function

- Decreased glomerular filtration rate
- Decreased renal plasma flow
- Decrease concentrating and diluting capacity

Noncompliance

"Keep watch also on the faults of the patients, which often make them lie about the taking of things prescribed." —Hippocrates.

Whenever multiple medications are prescribed, the risk of noncompliance is high. Table 3 defines the five categories of noncompliance. In a study evaluating 315 consecutive elderly patients admitted to an acute hospital, 28.2% of the admissions were drug related, 11.4% due to noncompliance, and 16.8% due to ADRs.[19] The reasons for noncompliance and polypharmcy are numerous. The elderly have increased introspection on body impairment and are more likely to use prescription and nonprescription medications on a regular and long-term basis. They may also have increased susceptibility to advertising of health foods and OTC medications. Direct to consumer advertisers in the United States spent $905 million in the first six months of 1999 alone.[20] These ads are targeted to people with chronic diseases and such a large-scale advertising campaign certainly contributes to the increasing cost of pharmaceuticals. Because they see multiple physicians with each visit, usually ending with a new or changed prescription, the elderly are at higher risk for confusion over proper medica-

Table 3. Types of Noncompliance

- Failing to take a prescribed medication
- Taking the medication for the wrong reason
- Taking more or less than the prescribed dose
- Taking medication at the wrong time or in the wrong sequence
- Taking the prescribed medication in combination with a potentially interactive medication that has not been prescribed

tion usage and are at greater risk for being prescribed duplicative or unnecessary medications. Many diseases commonly found in the elderly (such as hypertension and hyperlipidemia) foster noncompliance since these conditions often have no symptoms that prompt the patient to be compliant. Finally, because the elderly are more often hospitalized, each hospitalization tends to lead to frequent and confusing changes in drug regimens. Forty-five percent of discharge medications were started during hospitalizations. Table 4 lists some of the factors that have been associated with hospitalization secondary to poor compliance.

In treating elderly patients, one must be aware of the age-related changes that may uniquely affect compliance. Factors common in the elderly include impaired cognitive ability, musculoskeletal conditions that prevent them from opening a prescription bottle, and financial or transportation difficulties that may prevent drug acquisition. One of the worst acts of commission would be to continue escalating drug dosing when the real reason for the lack of a therapeutic effect is poor compliance.

Polypharmacy

"Polypharmacy is a prosthesis for the physician's incompetence. The less he knows, the more prescriptions he writes."—Zeljko Poljak, date unknown.

Office-based physicians write 100 million prescriptions per year for antibiotics. It is estimated that half of them are unnecessary. The cumulative effect of antibiotic resistance costs $30 billion annually. The American College of Physicians-American Society of Internal Medicine (ACP-ASIM) along with the Centers for Disease Control and Prevention (CDC) have taken an initiative to assist physicians in reducing unnecessary antibiotic prescribing.[21] Approximately 80% of patients can be reasoned with and dissuaded from antibiotic therapy for colds and other viral conditions.[22] The CDC has produced a form that looks like a standard "prescription pad" that can be used to give patients a written set of instructions for management of these viral conditions and identifies for the patient symptoms that would prompt further evaluation and the possible use of antibiotics. This form can be downloaded free of charge from the CDC's website: http://www.cdc.gov/ncidod/dbmd/antibioticresistance.

One of the banes of office practice are those patients who seem to be constantly asking for prescriptions for controlled substances such as narcotics, hypnotics, tranquilizers, and barbiturates. Although many times these requests are appropriate, having your patients sign a contract that identifies their responsibility and outlines a process for refills is a useful technique to reduce unnecessary prescribing and multiple phone calls to the office. An example of such a contract can be found at http://www.views.vcu.edu/vattc/contract.html.

Table 4. Factors Associated with Higher Risk of Hospitalization Secondary to Noncompliance[19]

- Poor recall of medication regime
- Seeing numerous physicians
- Female
- Medium income category
- Use of numerous medications
- Opinion that medications are expensive

Methods to Improve Compliance

"The young physician starts life with twenty drugs for each disease, and the old physician ends life with one drug for twenty diseases."—William Osler, 1903

The first step in improving compliance is to recognize that physicians do a poor job in identifying the poorly compliant patient. Although physicians commonly believe that patients do what we tell them to do, physicians tend to overestimate compliance in their patients.[23] General patient populations show a 43% noncompliance rate compared to 55% in the elderly.[24] Some methods to monitor compliance are listed in Table 5. However, one of the most commonly used methods is the "brown bag" approach. Simply ask your patients on a regular basis to bring in all their medications—prescriptions and OTCs—by all their doctors. Much can be learned by observing the dates the bottles were filled and by how many pills are left in each bottle. Bedell et al found in a study of 312 patients returning to a physician's office that 76% had discrepancies between their recorded medications and what they were actually taking.[25] On multivariate analysis, the two most significant predictors of medication discrepancy were patient age and number of recorded medications. This brown bag interview is also an excellent time to advise discarding or discontinuing medications that are no longer needed—sometimes called a "pharmacologic debridement." These opportunities allow you or your staff to update the patient's medication sheet, which can be easily copied and given to the patient for future reference. Recommending the use of color-coded medication boxes can help in keeping the patient on track. Pharmacists also often sponsor brown bag sessions at health fairs and at pharmacies and obviously serve as an excellent resource.

Always prompt patients for noncompliance with nonjudgmental questions such as, "People often have difficulty taking their pills for one reason or another.…Have you ever missed any of your pills?"[26] Asking your nurse to go over your patients' medication lists before you see them will be more likely to reveal compliance issues as patients often are more truthful and honest to your nurse than to the doctor. If your patients are not having the expected side effects or desired pharmacologic actions of a prescribed drug, think first about noncompliance as an explanation. An example would be a patient on a beta-blocker for hypertension who either does not have an improved blood pressure reading on subsequent visits or does not have the expected drop in pulse rate compared to before initiation.

Infrequency of dosing is one of the most important means to improve compliance. Cramer et al found that compliance for medications prescribed once, twice, three, or four times daily was 87%, 81%, 77%, and 39%, respectively.[27] Eisen et al reported compliance improving from 59.0% on a three-time daily regimen compared to 83.6% on a once-daily regimen.[28] Obviously, one must balance frequency of dosing with cost as

Table 5. Ways to Monitor Compliance[23]
• Direct observation of patients or by using nurse-administered medications
• Patient interviews
• Pill counts
• Pharmacy records to appropriate filling frequency
• Drug levels
• Drug markers
• Measurement of expected biologic effect
• Electronic medication dispensers

most once-daily drugs are usually more expensive brand names.

A simple but infrequently performed technique is to explain to patients the necessity of taking medications as prescribed and to give the patient written instructions. This method is particularly important in treating conditions such as hypertension and hyperlipidemia, which are often associated with poor compliance due to the absence of symptoms from these conditions. Some patients stop taking these medications without even informing their physician when their blood pressure or cholesterol is controlled, thinking that they no longer need them.

Some patients, especially the elderly, may have swallowing problems and may be best managed by alternative dosage forms such as liquids, patches, and injections. Some examples of commercially available patches are clonidine, nicotine, and estrogen.

Another principle, commonly called the geriatric law of pharmacy, is to start low and go slow. Most medicines are used to treat chronic diseases, and speed-to-dose escalation is not essential. One common example is the treatment of depression. Although rapid recovery is desirable, sometimes giving an elderly patient too high a starting dose will cause intolerable side effects that lead the patient to cease taking the remedy altogether. These patients return in 4-6 weeks to see the physician who, expecting to find clinical improvement, discovers that the patient stopped taking the antidepressant weeks ago and never bothered to call the office. Start with a low dose to minimize the risk of side effects and increase doses slowly. Stress with patients that if they have concerns about side effects, they are encouraged to call the office first to get advice as reduction in dosage or alternative agents are preferable to suffering unnecessary delay in response due to noncompliance.

Finally, consider the cost of medications. Patients who even casually mention that their medications are expensive are very likely to be noncompliant. Take their comments seriously and use the opportunity to further explore potential alternatives. The management of hypertension serves as an excellent example. The Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has recommended diuretics as one of the first-choice medications in the management of hypertension. Yet, the use of diuretics has steadily decreased over the last 15 years.[29] Physicians in office practices are never detailed by pharmaceutical representatives on generic drugs and, therefore, a selection bias for newer, more expensive drugs is created. About 2.2 million elderly patients spend more than $100 per month on prescriptions, and many pay far more.[30] Prescription drug expenditures grew at double-digit rates almost every year since 1980, climbing to 14.1% in 1997. In contrast, presumably largely due to the effect of health maintenance organizations (HMOs), total national health expenditures, hospital service expenditures, and physician service expenditures, growth rates decreased from about 13% in 1980 to less than 5% in 1997.[31]

Physicians tend to underestimate the cost of medications, especially that of brand-name and expensive drugs.[32] As a response to the very real cost of prescription medication for patients on fixed incomes, always consider a trial of medication withdrawal for those patients with chronic, stable conditions, especially when there is little scientific support for their continuance. For example, the benefits and risks of antihypertensive treatment in the very old (> 85 years of age) are uncertain, especially in a nursing home population where the risk of falls and postprandial hypotension is high.[33] The wisdom in taking such a laissez-faire approach is controversial and should be tempered with the potential risk of sequelae with their own associated costs.

Use generic drugs when possible and practical. Explore the use of samples or prescribing smaller quantities—particularly when instituting new therapy—so that any intolerable side-effects can be identified early and the drug can be discontinued without having large quantities of drug left over. Some manufacturers offer special programs for indigent patients falling below certain income levels. If possible, try to observe patients during their administration of eye drops and inhalers to be sure they exhibit good technique and are not wasting the drug. Education is obviously the keystone of therapy. The newest and most heavily advertised drugs are not always the best. Encourage your patients to call ahead to the pharmacy to inquire about pricing before ordering a drug the patient cannot afford and will not take.

Keeping Up-to-Date

For those physicians desiring more up-to-date knowledge on drug interactions and common adverse drug reactions, personal data assistants such as the PalmPilot (using free software packages like Epocrates from http://www.epocrates.com) are becoming increasingly available and practical for office use. Many hardbound and CD-based resources are widely and readily available.[34] HMOs using computerized databases for enrollees can be quite helpful for practitioners by identifying noncompliance and drug-drug interactions that might cause untoward side effects. HMOs and PBMs are also becoming valuable partners by being able to alert practitioners to those patients who may never have been prescribed scientifically validated therapies (i.e., beta-blockers for post-myocardial infarction or angiotensin converting enzyme inhibitors for congestive heart failure).

"A body yet distemper'd which to his former strength may be restored with good advice and little medicine."—William Shakespeare, Henry IV, Act 2.

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Physician CME Questions

5. Which of the following pharmacokinetic processes is least affected in the elderly?
   a. Absorption
   b. Volume of distribution
   c. Liver metabolism
   d. Renal excretion

6. Which of the following drugs is *not* affected by pharmacodynamic changes in the elderly?
   a. Warfarin
   b. Propranolol
   c. Gentamcin
   d. Isoproterenol
   e. Metoclopramide

7. Which of the following is *not* true in regard to phenytoin (Dilantin®)?
   a. Exhibits first order metabolism
   b. Drug levels should be done within three half-lives for monitoring purposes
   c. Induces the microsomal P450 enzyme system
   d. Highly protein bound

In Future Issues:

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