

Not Geropharmacotherapy I 01

Albert J Finestone¹
 Michael R Jacobs²
 John A Cacciamani¹

¹Institute on Aging, Temple University
 School of Medicine; ²Temple
 University School of Pharmacy,
 Philadelphia, PA, USA

Abstract: Critical to survival is the geriatric concept, allostasis, defined as the ability to achieve stability through change. It is appropriate that allostasis is an introduction to this commentary, which may partially apply to the medical and pharmacy profession as currently constituted.

Keywords: allostasis, pharmacy

Before writing a prescription, physicians must consider a number of factors including the pharmacodynamics and pharmacokinetics of the drug and how these might be affected by aging, polymedicine, adverse drug effects, and the potential for drug–drug interactions and patient nonadherence. As our knowledge of genetic polymorphisms associated with altered metabolism, drug distribution, and receptor affinity increase, it is likely that drugs which could not receive regulatory approvals in the past might now be approved for certain subsets of patients. Further complicating matters is the impact of direct consumer advertising, which increases consumer demand for products and services and may alter prescribing practices. This commentary will address these issues and make some suggestions for a partial solution.

With the increasing elderly population in the US, there are too few geriatricians. This has the result that most geriatric care is provided by primary care physicians who may not be familiar with or fully take into account the dynamics of aging on drug prescribing. In geriatric practice, as in any medical practice, the physician must consider the patient's gender, age, life style, (tobacco, alcohol, street drugs, or eating habits resulting in obesity); comorbidities, personality (adherence), any other prescription drugs, and over-the-counter drugs, including herbal medications taken by the patient (drug–drug interactions). In the geriatric population, however, the writing of a prescription is a far more complex procedure than many members of the medical profession recognize. This complexity is largely driven by the consequences of aging as briefly presented below. Several excellent reviews cover these topics in much greater detail (Bressler and Bahl 2003; Cafiero 2004; Goodman et al 2005; Petron and Katz 2005).

Pharmacokinetics involves absorption, distribution, metabolism, and excretion of drugs. Pharmacodynamics relate to a drug mechanism of action and its effect at the targeted receptor site, ie, what the drug does to the body. Depending on the drug, the aging process may have a significant effect on a drug's kinetics or dynamics (McLean and Le Couteur 2004). The physiology of aging with decreased body size and lean body mass requires decreased dosages. Increased body fat results in increased distribution of fat-soluble drugs. Decreased body water results in decreased distribution of water soluble drugs and finally decreased serum albumin produces an increased free fraction of drug in serum. These changes due to aging raise the potential for adverse effects. All of these factors significantly impact on the dosing of many drugs. Recognizing this impact has practical implications. First, initiating drug therapy at lower doses is usually appropriate for elderly patients. Second, patients

Correspondence: Albert J Finestone
 Institute on Aging, Temple University
 School of Medicine, 3420 North Broad
 Street, Philadelphia, PA 19140, USA
 Email afinesto@astro.temple.edu

may not tolerate a drug even at lower doses. Except in cases of true allergy, further dose reductions might improve tolerability and still offer a therapeutic benefit. It should be remembered that to be commercially viable drugs need to balance effectiveness with safety and there is little incentive to find the minimally effective dose. While this assures that the marketed dosage will demonstrate its therapeutic effect in the majority of recipients, it also results in some patients experiencing side effects because lower dose options are not available.

Alterations in organ function in the elderly can significantly alter dosing requirements. Let us start with the intake of medication in the gastrointestinal (GI) tract. In aging, there is decreased salivation, decreased gastric acidity, and decreased gastric emptying time. The upper GI tract usually has a clinically insignificant impact on drug therapy, except that diminished salivation and esophageal motility disorders may cause difficulty with swallowing drugs. Even this issue can be problematic as evidenced by the precautions related to bisphosphonate use in these patients.

In aging, there are alterations in phase I and II pathways of hepatic drug metabolism (Cotreau et al 2005). Phase II pathways convert drugs to metabolites which decrease, increase, or have no change in the action of the original drug. Phase I pathways convert drugs to inactive metabolites, which do not accumulate. With few exceptions; drugs metabolized by phase I pathways are preferred for older patients. Listing the drugs dealt with by phase I or II is beyond the scope of this paper. Cytochrome P450 enzymes, with the highest concentrations in the liver and small intestine, are a primary method of drug metabolism.

The role of these enzymes in hepatic drug metabolism is complex, but it is generally a good rule to decrease doses of hepatically metabolized drugs in elderly patients. The patient's concomitant therapy may interact with these enzymes to increase or decrease the effect of the drug the physician wants to add to the regimen. Even foods such as grapefruit juice can interact with these enzymes and result in dangerous, and at times life threatening, arrhythmias when combined with drugs such as erythromycin in a predisposed patient (Wilkinson 2005; Bressler 2006).

Significant decreases in renal function occur as we age with a very important impact on drug elimination. The glomerular filtration rate must decline to about one half the normal level before the serum creatinine concentration rises above the upper limit of normal. The Cockcroft-Gault formula can estimate creatinine clearance based on the age of the patient and the weight (Cockcroft and Gault 1976).

Creatinine clearance

$$= \frac{(140 - \text{age}) \times \text{lean body weight (kg)}}{\text{Plasma creatinine (mg/dl)} \times 72} \quad (1)$$

multiplied by 0.85 for females

Therefore, decreased doses in the elderly would be prudent, especially for those drugs where the parent compound or an active metabolite relies on renal elimination. Despite the availability of various methods to estimate renal function, it is not unusual for prescribers to look at a serum creatinine of 0.9 mg/dl in an elderly patient and conclude, "normal renal function".

Patients in the geriatric group frequently have a variety of chronic conditions requiring multiple medications and often receive care from several physicians. Furthermore, these patients may utilize several pharmacies increasing the risk for duplicative therapy and adverse drug reactions. This fact increases the risk of adverse drug effects when added to the previously discussed physiologic and pharmacologic changes in aging. In some instances the adverse effect may be misinterpreted by the physician as a new medical condition and result in a new prescription, which could result in additional adverse effects. Recently, Representative Patrick Kennedy, of Rhode Island, the son of Senator Edward Kennedy, had a bizarre adverse drug reaction in Washington. He awoke in the middle of the night and thought he had a vote to cast, dressed, and got in his car, and an automobile accident followed. Fortunately, no one was injured. The initial media reaction was he was drunk. His explanation was that he took a hypnotic to help him sleep with an antiemetic for gastroenteritis. This drug-drug interaction produced confusion and cognitive impairment and was a satisfactory explanation. Drug-drug interactions are not uncommon and all physicians should be aware of the possibility.

The seminal Institute of Medicine report (Kohn and Donaldson 1999) on patient safety provided extensive detail on medication errors and their sequelae as well as preventable adverse drug events in acute care but little was known about similar problems in ambulatory care. A recent report indicated these events in ambulatory care are common; many are preventable and many result in hospitalization (Thomsen et al 2007).

Problems occurred in cardiovascular drugs, analgesic, and hypoglycemic drugs, which are common drug classes used by the elderly (Goulding 2004; Schmader et al 2004; Gurwitz et al 2005; Simon et al 2005).

A related problem is poly-medicine, which is an excessive and inappropriate use of medications. Many elderly take 5 or more medications. Simply requiring all patients to

bring all medications including over-the-counter drugs and herbal medications to each office visit for the physician to review can reduce the potential for adverse effects. Patients usually will not inform their physicians of the use of herbal medications. With very few exceptions, none of these herbal medications have any more benefit when compared with available prescription drugs. Physicians must always consider an adverse drug reaction as a cause of a new symptom and avoid adding a new drug to treat the symptom rather than discontinuing a medication.

The other issue that the prescribing physician must consider is patient nonadherence to the medication. Obviously, a drug has no effect if it is not taken (Kulkarni et al 2006). The use of the term adherence indicates a relationship between the doctor and the patient so that the patient understands and is educated about the indications and action of the drugs. There are many reasons that patients do not take prescribed medications. Many drugs are expensive; side effects are objectionable, the patient does not understand how to take the drug or why the drug should be used at all.

The multiple factors described above make prescribing for the elderly patient difficult enough, but two more recent developments have the potential to make prescribing drug therapy in the elderly even more challenging. While seemingly unrelated they are in a sense polar opposites. The first is direct to consumer advertising of pharmaceuticals and the other is ethnopharmacology.

The United States and New Zealand are the only industrialized countries to allow direct-to-consumer advertising (Gellad and Lyles 2007). Although patients may benefit through increased disease awareness and increased adherence (Bradford et al 2006), this practice has the potential to increase healthcare costs, and may result in misunderstandings by the patients about their underlying disease and its management with poor use of clinic time (Bosic et al 2007). This is a serious problem in these days of managed care. Direct-to-consumer advertising of pharmaceuticals works best in certain circumstances. Of course, the advertiser must have an approved product that has been shown to be safe and effective. Generic equivalents should not exist and the condition being treated should be commonplace. The dosing regimen should be simple and it helps if certain advantages are identified over competing therapies (even if these exist only in the eyes of the advertiser). Since these conditions do not exist for a drug like warfarin, for example, it is unlikely that an advertising campaign will emerge despite the large number of potential beneficiaries. Since 2000 direct-to-consumer advertising of

prescription drugs has continued to grow both in absolute dollars and relative to other forms of promotion. Gaining a better understanding of the effects of this type of promotion has important public health implications not only for the US and New Zealand where such advertising is permitted, but for Canada and the European Union where such advertising is banned but has been subject to recent challenge (Bosic et al 2007).

The premise of individualized drug therapy is in contrast to the wide appeal that drives direct-to-consumer pharmaceutical advertising, ethnopharmacology, or pharmacogenomics (Burroughs et al 2002; Muonz and Hilgenberg 2005; Sadee and Dai 2005). The goal is to refine the drug use process to maximize the likelihood of response and minimize serious adverse reactions. As our knowledge expands in this arena it is likely that new drugs will be introduced to the marketplace that demonstrated inconsistent effectiveness or sporadic toxicity in the past. Their use may require the prescriber to genotype the patient prior to drug administration in order to avoid serious toxicities. Restricted access to these drugs may be required as is already done with products like cisapride, thalidomide, and clozapine.

Prescribing for the elderly has never been easy, and the likelihood is that it could be even more demanding. Some of the solutions to improving medication use already exist, but need to be more consistently implemented; others will require an overhaul of the drug distribution system.

A simple, but often underutilized approach is to have the patient "brown bag" all medications including "over the counter" medications and bring them to the office at every medical visit. The physician should make certain that the drugs prescribed are appropriate and have a known clinical use. Some medications that were started for an acute condition may no longer be needed. Others may no longer be providing an optimal response. Prescribers should always be open to discontinuing a medication or altering the regimen to achieve the best therapeutic outcome.

Electronic medical records with electronic transmission of prescriptions can screen for drug interactions and duplicative therapies; but are not yet widely available. Expert systems are being developed that facilitate safe dosing of medications based upon patient-specific parameters such as weight or organ function. With increasing use of these systems it will be important to remember that they only support the prescribing process and are no substitute for accurate histories and physical exams or clinical judgment.

To facilitate good therapeutic outcomes and reduce the possibility of unwanted events, physicians should collaborate

with all members of the patient care team. Specifically in regard to drug therapy, pharmacists offer a potentially valuable resource to assess and facilitate patient adherence with the prescribed regimen. In the US, federal requirements mandate that pharmacists offer counseling for newly prescribed medications. Patients should be encouraged by the prescriber to ask the pharmacist for this service. With the computerization of the dispensing function, it is likely that the patient's pharmacist has the most up-to-date list of medications and, based on refill records, can inform the physician if the patient is adherent with the drug regimen. Knowing the refill history the prescriber can more accurately evaluate the therapeutic response (or lack thereof). States require that pharmacists perform a prospective drug use review to identify potential drug interactions and other problems. Frequently these potential problems never materialize, but if they do the results could be disastrous.

In conclusion, writing a prescription is certainly not a simple procedure. Perhaps the best maxim to consider before you write a prescription is to think of what Vince Lombardi, the legendary coach of the Greene Bay Packers, said about throwing a football. He was a coach who believed in running the football and he said, "When you throw a football, three things could happen, and two of them are bad." Not a bad concept to have when writing a prescription.

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