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GERIATRIC PHARMACOLOGY: BASIC AND CLINICAL CONSIDERATIONS*

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INTRODUCTION

The fraction of the population over age 65 is growing at a rapid rate. The fastest growing group of people is the cadre over age 85 (1, 2). Age-related changes (3, 4) in physiological events, biochemical processes, and increased or decreased sensitivity of response are additive to the pathologic changes induced by the concomitant disease entities suffered by the elderly (5). Drugs given to rectify, ameliorate, or palliate, if prescribed in too large a dosage and/or too frequently, may significantly complicate the underlying changes induced by senescence and the pathological conditions for which the medications are being given (6, 7).

Basic and clinical research into the mechanisms of altered pharmacodynamics and pharmacokinetics provide data whose bottom line states, "lower dosage and lengthen dosing interval."

The basic geriatric research to support the aphorisms and dogma of geriatric clinical pharmacology forges the bridge connecting basic and clinical science.

To better understand the problems associated with therapeutics in geriatrics and to set the foundation for a discussion of basic research, we first discuss the significant changes associated with human senescence.

DRUG-INDUCED ALTERATIONS ASSOCIATED WITH THE PHYSIOLOGICAL CHANGES OF HUMAN AGING

Alterations in Body Composition

Physiological changes accompanying human aging include the following (8–10):

1. Increase in body fat
2. Decrease in fat-free mass (lean body mass)
3. Decrease in total body water.

Decreased hepatic albumin synthesis results in a lower serum albumin concentration, which may yield more free drug for entry to tissues or for access to elimination mechanisms (8, 11–13). For drugs with blood flow limited clearance, a gradual decrease in visceral blood flow reduces drug clearance through the liver or kidney (14–16). Due to these changes in body composition, a given dose of relatively water-soluble drugs—e.g. ethanol, acetaminophen, propicillin, antipyrine (17)—may result in higher blood concentrations and increased pharmacologic activity. Highly lipid-soluble drugs might have longer pharmacologic activity due to the increase in adipose tissue enhancing the storage of lipophilic drugs, such as diazepam, lidocaine, thiopental, tolbutamide, amitriptyline, thereby increasing the volume of distribution and delaying elimination (i.e. increasing their half-life) (18, 19).

Changes in Cardiovascular Function

In active, healthy elderly patients without ischemic heart disease (IHD), no significant change in resting cardiac output (CO) occurs. There is, however, less increase in heart rate in response to exercise, possibly as a result of a decrease in β-receptor sensitivity. Cardiac output is maintained by a rise in stroke volume and thus an increased force of cardiac contraction (Frank-Starling mechanism) (20–23). Thus, the healthy elderly heart at rest is characterized by the following:

1. Lower resting heart rate
2. No decline in stroke volume
3. Normal cardiac output.

Symptomatic and asymptomatic IHD, which is prevalent in older individuals in more developed countries, and hypertension can reduce ventricular function. Consequently, in many older individuals there is a gradual and asymptomatic reduction in CO associated with a gradual fall in blood volume

(23, 24). Diuretic-therapy, which causes acute volume contraction, may result in orthostatic hypotension and reduced organ perfusion. β-blockers and some calcium channel blockers (verapamil, diltiazem), given alone or in combination, can produce significant negative inotropic effects, thereby potentiating impaired ventricular function, resulting in heart failure.

Orthostatic hypotension may also result from a decreased preload due to venous pooling (nitrates) and thereby a reduction in CO after the administration of α-adrenergic blockers, such as prazosin, terazosin and doxazosin. Patients need to be instructed to sit up first and proceed slowly when going from a supine to a standing position while taking these drugs (25).

Tricyclic antidepressants and phenothiazines can have cardiac electrophysiologic effects similar to quinidine and may induce potentially lethal ventricular arrhythmias, especially in patients with IHD. Surveillance for prolonged P-R, QRS, Q-T_c, and reduced T-wave amplitude needs to be carried out to prevent development of arrhythmias (26). Reduction in maintenance dose by 50%, monitoring of plasma concentrations of the drug when available, and use of ambulatory ECG monitoring can minimize the likelihood of these adverse effects.

Patients receiving chemotherapy for cancer or leukemia may develop drug-related cardiotoxicity (27, 28). Doxorubicin can cause direct cardiotoxicity, affecting ventricular function and electrical conduction. The likelihood of these effects depends on the patient's age, pretreatment cardiac status, drug dose, and duration of therapy. Patients receiving doxorubicin should have baseline and follow-up radionuclide angiography, with periodic ambulatory ECG monitoring, and clinical assessment for heart failure.

Changes in CNS Function

Blood supply to the brain may be compromised by atherosclerotic narrowing of the vertebral and carotid systems. Hypothetically, this decrement in blood flow could cause neuronal loss and be responsible for the altered sensitivity to centrally acting drugs. Patients with Alzheimer's disease (25–31) and similar organic brain syndromes may exhibit altered sensitivity to highly lipid-soluble drugs that penetrate the CNS (e.g. β-blockers, central α-agonists, calcium channel blockers, tricyclic antidepressants, barbiturates, long-acting benzodiazepines, opiates) (31–34).

Although the cardiac and peripheral effects of central α agonists are beneficial, this class of drugs, such as clonidine and methyldopa can produce CNS side effects, e.g. lethargy, and can worsen underlying primary or secondary dementia processes. The relationship between the use of β-blockers, depressive reactions, and sleep disorders in the elderly appears to be convincing (32).

Changes in Reflex Responses

BAROCEPTOR REFLEX ACTIVITY As a result of decreased responsiveness and sensitivity of the baroreceptor reflex, patients may develop postural hypotension that is worsened when taking long- and short-acting nitroglycerin preparations, phenothiazines, diuretics, and dihydropyridine-type calcium channel blockers (nifedipine, nicardipine, felodipine), and peripheral α-blockers (prazosin, terazosin, doxazosin) (35–38).

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM Plasma renin concentrations and blood and urine aldosterone levels, both at baseline and in response to position and volume changes, decline with age, probably as a result of a decrease in sympathetic innervation to the juxtaglomerular cells (39, 40).

Similarly, in individuals with insulin-dependent diabetes and progressive renal insufficiency, there is a decrease in sympathetic tone to the juxtaglomerular apparatus, resulting in reduced renin concentration, angiotensin II, and aldosterone production, which may enhance Na^+ excretion and K^+ retention. The vulnerability of the elderly to hyperkalemia (41) may also result from coadministration of K-sparing diuretics or administration of drugs that suppress the renin-angiotensin system, e.g. nonsteroidal anti-inflammatory drugs [NSAIDs], β-blockers, and angiotensin-converting enzyme (ACE) inhibitors.

It has been suggested that because of lowered renin activity, elderly and black hypertensive patients may respond more readily to diuretics and calcium-channel blockers than to β-blockers and ACE inhibitors (42).

Fluid and Electrolyte Balance

As a result of intrinsic (see below) and diuretic-induced renal dysfunction, water retention (or loss) may occur, producing hypo- or hypernatremia (43–46). In addition, prostatic hypertrophy can result in obstructive uropathy, producing further postrenal deterioration in kidney function, water conservation, and hyponatremia, which persist until the obstruction has been relieved.

The use of diuretics can induce a vicious circle in which volume contraction stimulates thirst, leading to increased fluid intake. An individual may have access only to water, but insufficient solute to replace salt and other electrolyte losses, thus resulting in hyponatremia.

Normal fluid balance depends on an integration of cerebral, cardiopulmonary, excretory, and endocrine functions. Many chronic systemic diseases may produce hyponatremia due to a reduced renal ability to eliminate a water load (45, 46). The syndrome of inappropriate antidiuretic hormone (SIADH) activity has also been associated with a variety of drugs (see Table 1). Conversely, the drugs listed in Table 2 as well as certain cerebrovascular,

Table 1 Drug-induced SIADH and/or hyponatremia[a]

Chlorpropamide
Tolbutamide
Cyclophosphamide
Morphine
Barbiturates
Vincristine
Carbamazepine
Acetaminophen
Indomethacin and other NSAIDs
Chlorothiazide and hydrochlorothiazide
Hormones with mineralocorticoid and/or glucocorticoid effects (e.g. aldosterone, estrogen, progesterone)

[a] Adapted from Ref. 47.

renal, or adrenal diseases or hypertonic peritoneal dialysis may result in excessive water loss and hypernatremia.

Changes in renal and hepatic function are addressed in the section on pharmacodynamic-kinetic interrelationships.

With this background, we now examine the progress made in basic pharmacology research, and address altered mechanisms in aging that can explain clinical observations.

BASIC GERIATRIC PHARMACOLOGY

Receptor Responsiveness

Pharmacodynamic considerations include receptor number and affinity, signal transduction mechanisms, cellular responses, and homeostatic regulation. For a given dose, pharmacokinetic changes in senescence often result in a higher concentration of a drug at the target organ, whereas pharmacodynamic changes often result in a reduced cellular response for a given concentration of a drug. Some responses do not change in old age but may be altered earlier in

Table 2 Drug-induced water loss and hypernatremia[a]

Lithium	Glyburide
Alcohol	Propoxyphene
Demeclocycline	Amphotericin B
Phenytoin	Methoxyflurane
Acetohexamide	Povidone-iodine
Tolazamide	(principally H_2O loss from skin)

[a] Adapted from Ref. 47.

life, and there are few in which responsiveness actually increases (48). More often, however, responsiveness declines either over the entire life span or during the postmaturational phase. The variations may be explained by the different rates at which individual cells, tissues, and functions age. Only a few receptor systems have been examined in sufficient detail to attribute the loss of responsiveness with age to either changes in receptors or signal transduction (Table 3).

The first example is memory impairment in the rat. These age-related memory disturbances may involve deficits in central cholinergic neurotransmission (49). The impaired behavior parallels the loss of hippocampal pyramidal cell sensitivity to acetylcholine. There is a 15% decrease in muscarinic acetylcholine receptors with age; however, this small change in receptor density does not account for the much larger decrease in neuronal sensitivity (50). With age, however, these receptors are less able to couple to phospholipase C and stimulate phosphoinositol turnover (51). Thus, changes occur both in receptors and signal transduction with age (Table 3).

The second example is the decline in the absorption of calcium from the rat intestine. Calcium absorption is dependent on the conversion of 25-hydroxyvitamin D to the biologically active 1, 25-dihydroxyvitamin D in the kidney. This conversion is regulated by parathyroid hormone (PTH) and is decreased with age (52). The decline in responsiveness is apparently due to a decrease in the number of PTH receptors with age. PTH is coupled to the activation of adenylate cyclase, and PTH stimulation of adenylate cyclase decreases with age (53, 54). Postreceptor activation of adenylate cyclase by forskolin, however, is unchanged with age (53, 54), thus suggesting that receptor number is rate-limiting in the signal transduction process. Thus, PTH provides an example in which receptor number decreases with age but signal transduction is unaltered with age (Table 3).

The third example is the decline in myocardial responsiveness to catecholamines. Both the chronotropic and ionotropic responsiveness to β-adrenergic

Table 3 Selected receptor systems in rats whose physiological responsiveness decreases with age

Receptor	Tissue	Physiological change	Receptor density	Signal transduction	Reference
Muscarinic	Brain	↓ Memory	↓	↓	53
PTH	Kidney	↓ Activation of vitamin D	↓	↔	53, 54
β-Adrenergic	Heart	Rate and contractility	↔	↓	55
α_1-Adrenergic	Liver	↔Glycogenolysis	↓	↔	56, 57

agents decrease with age (59, 60). There are no changes with age in the density of β-adrenergic receptors in the heart (59), but the ability to activate adenylate cyclase is greatly reduced with age, and there are age-related impairments distal to the generation of cAMP (59, 60). This is an example of reduced responsiveness in which receptor density does not change with age, although decreases occur in signal transduction and in events distal to signal transduction (Table 3). This receptor system is discussed in greater detail below.

The last example is unique in that the physiological response, α_1 stimulation of glycogenolysis in hepatocytes, is unchanged with age (61). There is, however, a 39% decrease in the density of liver α_1-adrenergic receptors with age (56). In addition and more importantly, there is a 40% decrease in the number of high affinity receptors (56). Despite these substantial changes in total and high affinity receptors, α_1-adrenergic stimulation of phosphoinositide hydrolysis is unchanged with age (57). There is a correlation between target organ physiological response (glycogenolysis) and second-messenger activity (phosphoinositide hydrolysis) but no correlation between target organ response and coupled (high-affinity) receptors. This example demonstrates the presence of spare receptors. The loss of these spare receptors with senescence is a prime example of what is generally accepted as one of the most serious consequences of aging process, a loss of reserve capacity (55).

From the examples above, no generalizations can be made regarding the uniformity or direction of changes in receptors or signal transduction as a function of age. In particular, changes with age are both receptor- and tissue-specific. A specific receptor's subtype may remain unchanged, decrease, or even increase with age, depending on which tissue is investigated. In Table 4, receptor types are listed that either increase, decrease, or do not change with age without regard to the tissue of origin. Many receptors appear in two or even all three categories. Thus, receptor density often does not predict responsiveness. Signal transduction or cellular response may play a more important role in determining the pharmacologic effect of agents. From the examples discussed above, however, it is evident that no apparent correlation exists between any particular molecular event and the pharmacologic response.

Specific Receptors Studied in Aging Tissue

It is necessary to detail the changes at numerous points in the receptor-response pathway and to consider the homeostatic regulation of the pathway to understand fully the alterations of drug responsiveness with age. As an example, consider the signal transduction through α- and β-adrenergic receptors, which are among those best described with senescence. These receptors are part of a family of receptors that are characterized by seven membrane-

Table 4 Receptor concentrations with age[a]

Decrease	No change	Increase
Androgen	Androgen	Androgen
Estrogen	Estrogen	Estrogen
Insulin	Insulin	Insulin
Gonadotropin	Gonadotropin	Gonadotropin
Opioid	Opioid	Opioid
Benzodiazepine	Benzodiazepine	Benzodiazepine
α-Adrenergic	α-Adrenergic	α-Adrenergic
β-Adrenergic	β-Adrenergic	β-Adrenergic
Dopaminergic		Dopaminergic
Cholinergic	Cholinergic	
Glucocorticoid	Glucocorticoid	
Thyroid	Thyroid	
Prolactin	Prolactin	
Serotonin	Serotonin	
GABA	GABA	
	Epidermal growth factor	Epidermal growth factor
Glucogon	Low density lipoprotein	glutamate
Interleukin	Growth hormone	
PTH	Progesterone	
	Low density lipoprotein	

[a] See Refs. 53, 55, and 58.

spanning domains with the amino-terminus extracellular and the carboxyl terminus intracellular (62). The β_1- and β_2-adrenergic receptors are coupled to the activation of adenylate cyclase, whereas the α_2 receptor is linked to the inhibition of adenylate cyclase. Signal transduction between these receptors and adenylate cyclase is mediated by GTP-binding proteins (G proteins). These G proteins are part of a larger family of G proteins that provide signal transduction to a variety of specific effector enzymes and ion channels, including adenylate cyclase, phospholipase C, cyclic GMP, phosphodiesterase, Ca^{2+} channels, and K^+ channels (63–65).

It is apparent that G-proteins are involved in the action of many different hormones and drugs (63). Very little information is available about changes in G-protein function with age.

G-protein function has been quantified with age by a G-protein complementation assay in human erythrocytes (66) and rat heart (67). There was no change with age in G-protein function in erythrocytes, whereas in rat heart there was a decrease in function with senescence. A related study assessed G-protein function in rat heart with age indirectly by using stimulatory and inhibitory guanine nucleotide analogs to activate and deactivate G protein respectively (68). This study also found no change in G-protein function with age in the rat heart. Direct assessment of G-protein quantiation with age with

the recently available G-protein antibodies will be a fruitful area of research in the future.

The cardiovascular system is one of the most important organ systems in which responsiveness decreases with age (20–23). In addition to a decline in chronotropic and ionotropic responses to β-adrenergic agents in the rat heart described above, age-related decreases occur in α_2-adrenergic mediated vasoconstriction in the rat (69), in the chronotropic response in heart in man (70), and β-adrenergic smooth muscle relaxation in man (71). A number of studies have examined changes in β and β_2-adrenergic receptor density and signal transduction with senescence (55). The age-related changes in β-adrenergic receptor numbers are tissue-specific. The density of receptors declines in the rat brain, white adipocytes, brown adipocytes, and erythrocytes but not in rat heart or lung or in rat or human lymphocytes (Table 5). More importantly, signal transduction almost universally declines, as manifested by a reduction in the ability to stimulate cAMP (53, 72). This decline

Table 5 α- and β-Adrenergic changes with age[a]

Species and tissue	Receptor	Physiological responsiveness with age	Receptor density with age	Signal transduction with age	References
Rat myocardium	β,β_1,β_2	↓	↔	↓	53, 72
Rat cortex and cerebellum	β,β_2		↓ ↔	↔	73
Rat white and brown adipocytes	β_1	↓	↓	■	74, 75
Human heart	β	↓			70
Human lymphocyte	β_2		↔ ↑	↓	77–79
Rat heart	α_1	■	↓	↓	76, 80–82
Rat liver	α_1		↓	↔	56, 57
Rat vasculature	α_1	↔	↔	↑	72, 83
Rat heart	α_2	↓			84
Rat vascular	α_2	↓			85
Human platelet	α_2		↑ ↓ ↔		85

[a] For review see Ref. 55.

is mostly due to a reduced ability to couple to stimulatory G protein and a decrease in the activity of the catalytic unit of adenylate cyclase (53, 67). Data on changes in α-adrenergic receptors are sparse and conflicting. The α_2 subtype is linked to the inhibition of adenylate cyclase, and α_2 receptor density is either reduced, increased, or not changed in human platelets (85). Responsiveness to α_2-adrenergic stimulation in most rat tissues, however, is markedly reduced by aging (69). The α_1-subtype activates phospholipase C, and the density of this receptor subtype is reduced in rat heart and liver but not in smooth muscle (Table 4). Stimulation of phospholipase C activity through the α_1 receptor is reduced in rat heart but not liver (Table 5).

Adaptation Responses in Aging Tissues

HEART From the above discussion, it is clear that adrenergic receptor and post-receptor mechanisms are altered with age in some tissues. Equally important in explaining the age-related changes in sympathetic responsiveness is the availability of catecholamines; this availability is governed by a complex series of mechanisms, including catecholamine biosynthesis, storage, release, uptake, and metabolism. These changes are discussed in the section on age-related changes in the pharmacokinetic parameters.

Catecholamines self-regulate the responsiveness of the β-adrenergic stimulatory pathway (86). An important aspect of this self-regulation is desensitization of the β-adrenergic receptor. Following agonist binding to the receptor and activation of adenylate cyclase, the receptor is left in the uncoupled state. This event is associated with phosphorylation of the receptor by a specific kinase. Functionally, the receptor expresses low affinity binding for the agonist, and there is a decrease in the ability of agonist further to stimulate adenylate cyclase. A portion of the cell surface receptors are internalized during the desensitization process (receptor downregulation). These internalized receptors are sequestered in membrane vesicles that are distinct from the plasma membrane and contain the other components of the adenylate cyclase complex (86).

The up- and downregulation of the β-adrenergic receptor with age has been investigated in three organ systems: rat heart, rat brain, and human lymphocytes. Though the density of β-adrenergic receptors does not decrease with age in the rat heart, it has been suggested that homeostatic regulation of this receptor may be impaired with senescence. Treatment with β-adrenergic antagonists induces supersensitivity, whereas treatment with β-adrenergic agonists leads to catecholamine refractoriness. Upregulation of β-adrenergic receptors occurs in hearts from older rats (87). Both subtypes of cardiac β-adrenergic receptors participate in the upregulation response to chemical denervation by 6-hydroxydopamine regardless of age (88). Similarly, the upregulation of β-adrenergic receptors in the rat heart in response to thyroid

hormone administration is also unchanged with age. Receptor density increased twofold in hearts from 3-, 12-, and 24-month-old rats (89). The downregulation of cardiac β-adrenergic receptors also occurs equally in younger and older rats exposed to the receptor agonist, metaproterenol (90). In another study, Tumer et al (91) investigated the effect of decreased adrenal medullary catecholamines due to adrenal demedullation on the regulation of postjunctional cardiac β-adrenergic receptors with age. Surprisingly, adrenal demedullation downregulated cardiac β-receptor number, but this downregulation of β-receptors was unaffected by age (91). In contrast, the rate of β-adrenergic receptor regeneration after irreversible blockade is slower in senescent compared with young rats (92). The rate of upregulation and recovery from downregulation with age has not been studied, however. A slower rate of response might compromise the capacity of the heart to respond to homeostatic challenges.

BRAIN In contrast to the heart, in the rat brain β-adrenergic receptor density is reduced in senescence (93). Weiss et al (93) have investigated two models of supersensitivity (light-induced and reserpine-induced) and showed that light exposure produced a significant increase in β-adrenergic receptors in pineal glands of young rats, but not in those of aged rats. Although repeated doses of reserpine increased β-receptors significantly in the pineal glands, cerebral cortices, and cerebellums of young rats, the response to reserpine in aged rats was abolished in the cerebral cortex and the cerebellum and significantly reduced in the pineal gland. Greenberg et al (94) have also studied β-adrenergic receptor subsensitivity in the rat brain following desmethylimipramine administration, which blocks the reuptake of norepinephrine into sympathetic nerve endings, thereby increasing the availability of catecholamines. These investigators reported desmethylimipramine significantly reduced the number of β-adrenergic receptors in both young and senescent rat cerebral cortex and pineal gland but not in the cerebellum, thus suggesting that aged animals have an equal ability to downregulate in response to catecholamines following increased adrenergic input. There seems to be a difference between the capacity of β-adrenergic receptors to upregulate in aging heart and brain, whereas the downregulation with age is unaltered in both tissues.

LYMPHOCYTES The majority of the studies on human lymphocytes have reported no changes in β-adrenergic receptors with age (55). Recently, one report indicated an increase in receptor number with age (79). Studies on the regulation of lymphocyte β-adrenergic receptors have been sparse. One study indicated that upright posture induces an acute increase in receptor density in young subjects that does not occur in older subjects (95). Thus, in the human

lymphocyte, upregulation is impaired with senescence. This finding is in contrast to the rat heart and similar to the rat brain, where upregulation is impaired as a function of age.

In summary, pharmacodynamic changes with age include receptor alterations, impaired signal transduction, and decreased homeostatic regulation. An additional consideration is that the plasma concentration of certain hormones and neurotransmitters such as PTH and norepinephrine increases with age. Some of the changes in receptors and post-receptor mechanisms may be a result of homeostatic regulation by increasing hormone and neurotransmitter concentrations with age (for reviews see 53, 55). Thus, the effect of a given age on pharmacologic responses is difficult to predict. A thorough examination of the principles discussed above contributes to our understanding of clinical therapeutics in the elderly. It is clinical studies, however, as discussed below, that provide the guidelines for treatment of the elderly.

PHARMACODYNAMIC–PHARMACOKINETIC INTERACTIONS IN CLINICAL GERIATRIC PHARMACOLOGY

Absorption

Absorption of food and drugs remains unaltered in elderly patients with an intact gastric mucosa, despite increased gastric pH and reduced GI blood flow (96). Nonetheless, absorption may be altered by nutritional deficiencies (e.g. of vitamin B12 or intrinsic factor), partial gastrectomy, and drug interactions with laxatives, antacids, and agents that decrease gastric emptying (97) (e.g. anticholinergics or anti-Parkinsonians). Kaolin-pectin, antacids, and iron inhibit the absorption of tetracycline; antacids can decrease the bioavailability of digoxin by 25% (96, 98). In general, the rate and extent of drug absorption from the gastrointestinal tract is unchanged in the elderly. The support for this statement is based on bioavailability studies by Simon et al (99) and Cusack et al (100).

Oral bioavailability (f), the fraction of absorbed drug that reaches the systemic circulation in unchanged form, can be calculated from the ratio of dose-normalized areas under the curve (AUC) following oral dosing and iv dosing (101–103). Clinically significant alterations in bioavailability of propicillin, digoxin, or theophylline were not observed in the elderly. Cusack et al (100) did conclude, however, that the mean absorption rate of theophylline was significantly greater; the clinical significance of this information is unknown, however. Another factor that must be considered when drugs are given orally is "first pass" metabolism whereby metabolism of the drug occurs during passage through the portal circulation or within the gut wall (101–103). Oral bioavailability refers to the amount of drug reaching the systemic circulation following oral dosing and is determined by absorption and hepatic

removal by first pass metabolism. Thus, if hepatic removal, expressed as an "extraction ratio" is high, a relatively smaller proportion of an orally administered drug may reach the circulation in unchanged form. Chlormethiazole (104), propranolol (105), metoprolol (106), labetalol (107), and verapamil (108) have all been studied in the elderly and demonstrate an increase in bioavailability as a consequence of a reduction in first-pass hepatic extraction. Rubin et al (15) studied prazosin in the elderly and found a significant reduction in bioavailability resulting in less unchanged, active drug reaching the systemic circulation. They concluded that gastrointestinal absorption of prazosin is likely to be reduced in the elderly.

Studies with levodopa and clorazepate have revealed evidence for changes in intragastric metabolism in the elderly. Evans et al (109) have shown a reduction in the gastric wall content of dopa decarboxylase. This has resulted in a threefold increase in the availability of levodopa in the elderly.

Aging and antacids elevate gastric pH. Antacids bind clorazepate and this has been demonstrated to result in reduced plasma concentrations of desmethyldiazepam (110, 111). The pharmacodynamic effect of the desmethyldiazepam is therefore reduced.

Distribution

The changes in body composition mentioned above affect drug distribution (101–103). From the perspective of clinical pharmacokinetics, the extent of distribution of a drug is determined by its molecular size, lipophilicity, acid/base properties, and binding of the drug to plasma albumin and tissue proteins. The volume of distribution, a theoretical rather than an actual volume, relates the total amount of drug in the body to the serum or plasma concentration (101–103). It therefore can be used to design dosage regimens that employ loading oral doses or intravenous bolus administration. Albumin, whose volume of distribution is slightly greater than plasma volume, exhibits very little extra-vascular distribution. With the changes observed in body composition, and the resultant alterations in volume of distribution in the elderly, one can better interpret plasma half-life determinations. Plasma half-life varies inversely with clearance; and plasma half-life may be prolonged by an increase in the volume of distribution independent of any reduction in clearance

$$\left[T\ \frac{1}{2} = \frac{0.693 \times V_d}{\text{clearance}}\right].$$

Steady-state plasma concentrations of a drug are dependent on the dosage and inversely related

$$\left[C_{ss} = \frac{F \times \text{dose}}{\tau \times \text{clearance}}\right]$$

(102) and clearance. As a result of a reduction in clearance the plasma half-life of a drug is prolonged and the steady-state concentrations will increase. On the other hand, if the plasma half-life is prolonged due to an increase in the volume of distribution, there will be no increase in mean steady-state concentrations because mean CP_{ss} is independent of the volume of distribution. Thus the consequences, if any, of an increase in drug concentration may not be seen. There would be an increase, however, in the time to reach steady-state concentrations. As a result of the publication by the Food and Drug Administration of the guidelines dealing with studying drugs in the elderly, further data will now accrue that will include measurements of volumes of distribution, clearances, and steady-state concentrations in the elderly for a greater number of drugs (112).

For the majority of protein-bound drugs, the free (unbound) fraction is available for pharmacodynamic action, metabolism, and elimination (101–103). When there is a small reduction in the protein binding of extensively bound drugs, the proportional increase in free drug concentration can be clinically significant. If through drug interaction, aging, or renal or hepatic failure, a significant increase in free-fraction results, the pharmacodynamic response would be enhanced.

To summarize, the effects of drug binding with low tissue distribution, i.e. V_d is similar to plasma volume, can include (*a*) an increase in free concentration, (*b*) an increase in the elimination rate by means of metabolism or excretion, (*c*) an increase in pharmacodynamic response related to the rise in free concentration, (*d*) an increase in the volume of distribution and a reduction in total plasma concentration. These are the results anticipated after single-dose administration (101–103). With chronic dosing, an increase in the elimination rate can reverse the other changes except for changes in V_d, thereby decreasing the augmented pharmacodynamic action. To summarize the effect of drugs with extensive tissue distribution, i.e. highly lipid soluble drugs the following may be observed: (*a*) a significant rise in the volume of distribution and a reduced total plasma concentration, (*b*) little if any effect on free plasma concentration, elimination rate, or pharmacodynamic effect, and (*c*) altered relationship during steady-state concentration between total and free steady-state concentrations (101–103).

Jusko & Gretch (113), Sjöqvist et al (114), and Mitchard (115) have reviewed these principles and have emphasized that any decrease in the binding characteristics of avidly bound drugs can effectively lower the normal therapeutic range. This has direct implications in therapeutic drug monitoring

of commonly used agents. Plasma protein binding may be reduced as a result of a reduction in plasma albumin, the major binding protein, or as a result of changes in binding affinity due to aging. Acidic drugs that are highly protein bound will have less affinity for binding to albumin, i.e. in renal failure or aging resulting in more free drug available for (*a*) tissue distribution, (*b*) pharmacologic activity, and (*c*) elimination (see Table 6; 12, 116, 117). Weakly acid organic compounds (118–120), e.g. salicylates, barbiturates, warfarin, theophylline (100), tolbutamide, and sulfonamides, bind principally to plasma albumin. α_1-Acid glycoprotein (AAG) (121, 122), on the other hand, binds mostly lipophilic cationic (basic) drugs. AAG tends to increase with age, and with acute and chronic inflammation. The binding of drugs to AAG is increased during acute illnesses such as myocardial infarction (MI) (123, 124). In the setting of MI, lidocaine or propranolol given for prophylaxis against arrhythmias may be more avidly bound to AAG, thus yielding a decrease in the fraction of free drug. When the concentrations of AAG return to normal over a period of weeks to months, binding of these basic drugs also returns to normal. Drugs bound to α_1 AG can exhibit nonlinear protein binding and hence a reduced free fraction (see below).

Metabolism and Changes in Hepatic Kinetic Function

The ability of the liver to metabolize drugs does not decline similarly for all pharmacologic agents with advancing age (125, 126). The most frequent changes involve the microsomal mixed-function oxidative system (phase I oxidation and reduction), but little or no change occurs in the conjugative processes (phase II conjugation) (see Table 7). Changes due to hepatitis or, more commonly, a decrease in hepatic blood flow as a result of heart failure may also impair the ability of the liver to metabolize drugs.

As an example, if elderly patients receiving β-blockers, which decrease CO and hepatic blood flow, concomitantly receive lidocaine, the resulting drug

Table 6 Drugs whose reduced plasma protein binding in the elderly may result in adverse reactions[a]

Warfarin	Phenylbutazone
Diazepam	Tolbutamide
Lorazepam	Meperidine
Phenytoin	Disopyramide

[a] Adapted from Refs. 118–120.

Table 7 Drugs whose hepatic metabolism is reduced in the elderly[a]

Phase I (preparative) reactions	Phase II (synthetic) reactions
Oxidation	
Hydroxylation	(Essentially unchanged in the elderly)
Alprazolam	Conjugation
Antipyrine	Acetylation
Barbiturates	Methylation
Carbamazepine	
Ibuprofen	
Imipramine	
Desipramine	
Nortriptyline	
Phenytoin	
Propranolol	
Quinidine	
Warfarin	
Dealkylation	
Amitriptyline	
Chlordiazepoxide	
Diazepam	
Flurazepam	
Diphenhydramine	
Lidocaine	
Mepcridine	
Theophylline	
Tolbutamide	
Reduction	
Nitroreduction	
Nitrazepam	

[a] Adapted from Ref. 154.

interaction leads to a decrease in lidocaine clearance. As a result, lidocaine toxicity can occur (127).

Although liver size and blood flow decline with advancing age, routine tests of liver function yield normal results in the absence of disease. This reflects the current inability to quantify hepatic function (127). As a consequence of reduced metabolism, certain drugs that are cleared by the liver may require administration in lower dosages to avoid accumulation and excessive pharmacologic effects (125).

In general, drugs with *low hepatic extraction* have a high volume of distribution, a reduction in clearance, and a prolongation of the elimination half-life. Drugs in this class can be divided into those involving Phase I reactions and Phase II reactions. The marker drug, antipyrine, is an excellent model for studying the microsomal mixed-function, oxidase-drug-metabolizing system within the liver. In the elderly, O'Malley et al (125),

Vestal et al (17), Swift et al (18), and Wood et al (19) have shown a prolongation of antipyrine plasma half-life and a decrease in its metabolism clearance. These results probably stem from a slow hydroxylation process in the liver. In the case of imipramine that is demethylated to desipramine, a significant prolongation in the elimination half-life and a reduction in plasma clearance has been demonstrated (125). This may be a consequence of a slower rate of demethylation, greater volume of distribution, and a reduction in plasma clearance. Abernethy et al (128) suggested that microsomal demethylation reactions, as in imipramine metabolism, may be more sensitive to changes related to age than the effect of hydroxylation on desipramine metabolism.

Examples of drugs with low hepatic extraction or clearance involving Phase II reactions have been less extensively evaluated in the elderly (Table 6, 7). Acetaminophen is conjugated through glucuronide and sulphate pathways. No change has been found in the rates of conjugation in the elderly with acetaminophen (129). On the other hand, acetylation by acetyl transferase was studied by Gachalyi et al (130), who found that the number of slow acetylators in a group of older individuals was much greater than that found in a population of younger individuals.

By contrast, drugs with high hepatic clearance or extraction are those in general with a high first pass effect or presystemic clearance (131). The drugs that demonstrate this best are lidocaine (14), prazosin (15), and propranolol (16, 105). These drugs have been studied in the elderly. Although there is a prolongation of plasma half-life of lidocaine, propranolol, and prazosin, it is based more on an increase in their volumes of distribution than on any other kinetic parameter (102).

Relevant to understanding hepatic metabolic changes with age is the concept of protein-binding-sensitive and protein-binding-insensitive hepatic clearance (101–103, 131). For total drug, hepatic clearance can be expressed as a function of hepatic blood flow (Q_H) and extraction ratio. Extraction ratio (E) can be expressed as a function of intrinsic clearance, where clearance is the intrinsic clearance of the fraction of free drug (f) and $f\,Cl_i$ is the intrinsic clearance of total drug, i.e.,

$$Cl_H = Q_H \times E;\ E = \frac{f\,Cl_i}{[Q_H + f\,Cl_i]};\ Cl_H = \frac{Q_H \times f\,Cl_i}{[Q_H + f\,Cl_i]}.$$

Theoretically, it can be seen that for total drug, an increase in f results in an increase in hepatic clearance. For a flow-limited drug, where intrinsic clearance is greater than hepatic flow, there is very little effective increase in clearance by increasing the free drug fraction, since hepatic clearance is approximately equal to the hepatic blood flow. Thus the clearance of flow

limited drugs can be said to be *binding-insensitive*. For a capacity-limited system, where intrinsic clearance is less than hepatic flow and hepatic clearance is approximately equal to $f Cl_i$, increasing f can have a significant effect on clearance, depending on the normal binding. Thus, if normal binding is 95%, that is $f=0.05$, then a reduction in protein binding to 90% will double f and the resultant clearance will approach doubling. In this case the clearance is *binding-sensitive*. If the normal protein-binding were 40% ($f=0.6$), a reduction in protein-binding to 30% would have relatively little effect on clearance and the clearance could be considered binding-insensitive (101–103, 131).

If a drug is capacity-limited ($E < 0.3$ at normal Q_H), then a decrease in protein binding of a binding-sensitive drug could result in the following sequence: (*a*) f increases with a resulting increase in volume of distribution of total drug and in clearance; (*b*) the increased clearance nullifies any resulting increase in $f Cl_i$ and has a more significant effect on elimination rate than the increased volume of distribution; (*c*) the concentration of total drug decreases, the concentration of free drug remains the same. The condition exists, therefore, for a decreased measured (total) drug concentration with no accompanying change in pharmacodynamic response (101–103, 131).

If a drug is flow limited ($E > 0.3$ at normal Q_H), then a decrease in protein binding of a drug can result in the following sequence: (*a*) f increases, with a resulting increase in volume of distribution of total drug and no change in clearance; (*b*) the increased volume of distribution results in a decreased elimination rate, thereby nullifying the decrease in total drug level due to the conversion of bound drug to free drug and the movement of part of that to the periphery; (*c*) the concentration of free drug rises, the concentration of total drug remains the same. The conditions exist therefore for an increase in pharmacodynamic response associated with no apparent change in measured (total) drug level (101–103, 131).

In summary, when there is a decrease in plasma protein binding, the fraction of free drug in plasma increases and is reflected as either: (*a*) a decrease in total drug concentration and no change in free drug concentration (capacity-limited) or binding-sensitive with no change in pharmacodynamic response; (*b*) no change in total drug concentration and an increase in free-drug concentration (flow-limited or binding-insensitive) with an increase in pharmacodynamic response; or (*c*) a combination of the two (101–103, 131).

Because these principles impact on the elderly who may be receiving multiple drugs in the setting of a decrease in hepatic blood flow, and wherein they may be receiving drugs such as lidocaine, phenotoin, propranolol, or salicylates, the therapeutic interpretation of a blood level in the setting of a decrease in protein binding must be made cautiously and related to the clinical

Table 8 Drug interaction and hepatic function[a]

Primary drug	Interacting drug	Pharmacokinetic mechanism	Pharmacodynamic effect
Effect enhanced			
Warfarin	Phenylbutazone	Inhibition of drug metabolism	Hemorrhage
	Metronidazole	Inhibition of drug metabolism	Hemorrhage
Sulfonylurea hypoglycemics	Chloramphenicol	Inhibition of drug metabolism	Hypoglycemia
Benzodiapepines	Cimetidine	Inhibition of drug metabolism	Excessive sedation
Theophylline	Cimetidine	Inhibition of drug metabolism	GI upset, arrhythmias, seizures
Effect decreased			
Warfarin	Barbiturates, rifampin, disopyramide	Induction of drug metabolism	Loss of anticoagulation
Prednisone	Barbiturates	Induction of drug metabolism	Loss of antiallergic and anti-inflammatory properties
Quinidine	Barbiturates	Induction of drug metabolism	Loss of antiallergic and anti-inflammatory properties
Propranolol	Tobacco (cigarette smoking)	Induction of drug metabolism	Loss of BP and heart rate control
Theophylline	Tobacco (cigarette smoking), phenytoin, rifampin	Induction of drug metabolism	Loss of bronchodilatation

[a] Adapted from Refs. 139 and 154.

setting and patient's response. Decreased hepatic clearance of the following drugs has been shown: benzodiazepines flurazepam, alprazolam, chlordiazepoxide and their active metabolites (desmethyldiazepam, desalkyflurazepam), quinidine, propranolol, lidocaine, and nortriptyline (7, 132–137).

The clinical effects of a reduction in diazepam clearance are greater sedation and possibly iatrogenic pseudodementia. Flurazepam accumulation can produce prolonged sleep. This response is age- and dose-related. Although men clear diazepam and several metabolites more slowly than women do, the difference is not clinically significant (132–137).

Hepatic induction and inhibition *have not* been studied extensively in the elderly (Table 8). Wood et al (19) have studied the effects of smoking on antipyrine clearance in elderly individuals. They found an age-related decline in antipyrine clearance in those subjects who smoked. They concluded that reduced cigarette consumption in the elderly and a likely reduction in the capacity of hepatic enzymes to be responsive to the inducing effect of tobacco

Table 9 Drugs whose renal elimination is reduced in the elderly[a]

Digoxin
Aminoglycoside antibiotics
Atenolol, nadolol
Lithium
Diuretics
Procainamide, tocainide, disopyramide
Clonidine, guanfacine
NSAIDs
Ranitidine, famotidine
Captopril, enalapril, lisinopril

[a] Adapted from Refs. 47, 139 and 154.

may be important factors. In a later study, Twum-Barima et al (138) studied the interaction between antipyrine and rifampin. Rifampin is a potent inducer of microsomal enzyme activity. In elderly male subjects, there was no significant effect on antipyrine half-life when rifampin was introduced. Nevertheless, there are conflicting data with regards to changes in the aging liver's response to enzyme induction (18, 140). Pearson & Roberts (141) have shown that glutethimide resulted in an increase in antipyrine clearance. Conversely, Divoll et al (142) have shown that the enzyme-inhibiting action of cimetidine had no effect on the clearance of antipyrine and desmethyldiazepam.

Antibiotics (e.g. cloxacillin, nafcillin, ampicillin, oxacillin) and cephalosporins (e.g. cefoperazone and ceftriaxone) are excreted unchanged by the biliary system and in some cases are reabsorbed in the small intestine, via the enterohepatic circulation. Biliary tract surgery and chronic pancreatic disease may alter biliary excretory and enterohepatic recirculatory functions. The following results have been observed:

1. Reduced liver mass.
2. Redistribution of regional blood flow from liver.
3. Decreased hepatic microsomal enzyme activity.
4. Reduced plasma albumin due to decreased hepatic production.

Elimination and Changes in Renal Function

Biotransformation of drugs in the liver produces polar metabolites, which are then excreted in the urine or feces (via the biliary system).

Drugs such as digoxin, lithium, angiotensin-converting enzyme inhibitors, and aminoglycoside antibiotics, which are minimally metabolized, are eliminated predominantly unchanged by the kidney (143, 144).

Beginning with the fourth decade of life, there is a 6 to 10% reduction in

GFR and renal plasma flow per decade (145). Thus, by age 70 a person may have a 40 to 50% decrease in renal function, even in the absence of kidney disease. Hypertension, common in this population, is associated with nephrosclerosis, which may produce parenchymal disease and an even greater reduction in renal function (5).

Drugs that are eliminated substantially by renal excretion (see Table 9) should be given in reduced doses or less frequently to avoid accumulation and untoward pharmacologic effects (144).

Dosage adjustment of renally excreted drugs can be based on an estimate of creatinine clearance, as follows (146):

$$\underset{\text{(mL/min)}}{\text{Creatinine clearance}} = \frac{(140 - \text{age}) \times \text{body weight (kg)}.}{72 \times \text{serum creatinine (mg/dL)}}$$

For women, multiply by 0.85 (10).

Because drugs may compete for the same specific site of renal secretion, elimination of one drug may be impaired by the concurrent administration of another (147, 148). Examples are presented in Table 10.

Generally, drug accumulation increases pharmacologic effect; however, although furosemide accumulates as renal function declines, its efficacy is reduced. Because furosemide and other diuretics act on the luminal side of the renal tubule, their access to this site of action is reduced as renal function declines. Thus, more furosemide may be required to produce the desired diuretic response (149, 150).

Finally, some drugs provoke azotemia. For example, tetracycline inhibits protein synthesis, provoking a catabolic effect, whereas glucocorticoids are directly catabolic; thus, both can elevate blood urea nitrogen (BUN). Cimetidine and trimethoprim interfere with creatinine excretion (47), thereby elevating serum creatinine. Aminoglycoside antibiotics have the potential to cause nephrotoxicity and ototoxicity, but careful monitoring of the dose and dosing interval may prevent the nephrotoxicity.

Tissue Responsiveness (Sensitivity)

The levels at which changes result in altered responsiveness to drugs may occur at (*a*) receptor, (*b*) postreceptor (biochemical, structural, translation), (*c*) tissue/organ, (*d*) homeostasis.

Aging may result in changes in receptor density or characteristics, especially sensitivity to catecholamines. Receptors are in a dynamic state and receptor numbers can be altered rapidly in terms of up or downregulation by both physiological and pathological processes and by drugs. Signal transduction has been addressed above as have alterations in tissue responsiveness to biochemically initiated sequences involving cyclic AMP in laboratory an-

Table 10 Drug interaction and renal function[a]

Primary drug	Interacting drug	Mechanism	Clinical effect
Digoxin	Quinidine	Inhibition of renal and nonrenal clearance; volume of distribution	Digoxin toxicity
	Verapamil	Inhibition of renal and nonrenal clearance	Digoxin toxicity
	Spironolactone	Inhibition of renal and nonrenal clearance; volume of distribution	Digoxin toxicity
Methotrexate	Aspirin	Inhibition of renal excretion	Bone marrow depression
Penicillin	Probenecid	Inhibition of renal excretion	Penicillin accumulation
Quinidine	Sodium bicarbonate	Inhibition of renal excretion	Quinidine intoxication producing wide QRS complex

[a] Adapted from Refs. 47, 139 and 154.

imals. Clinical examples of altered tissue responsiveness are of critical importance in clinical geriatric pharmacology.

Elderly patients tend to exhibit enhanced responses to CNS-active drugs, attributed to a greater tissue sensitivity (6, 152–154), as well as the altered pharmacokinetics described above. Changes in cognition due to aging or disease are difficult to segregate from those due to drugs. Nevertheless, drug-induced dementia has been well described and recently reviewed (155). For example, in haloperidol and metoclopramide are more likely to cause extrapyramidal syndromes, and meperidine may produce respiratory depression. Although not well understood, the use of propranolol for hypertension or ischemic heart disease in the elderly has been related to sleep disturbances, including nightmares (156).

Studies have shown an increase in sensitivity to oral anticoagulants. Patients over age 70 have been shown to require a dose of warfarin 50% of that given to persons 40–60 years old (157). Although these data were refuted by Jones et al (158), the presence of multiple diseases interacting with multiple drug regimens mandate that lower average dosages be recommended for warfarin.

The dosage of heparin is not significantly affected by age, but bleeding reactions seem to be more common in women (159).

In some instances, patients may exhibit a decreased rather than exaggerated response at the tissue level. Such is the case with β-blockers (70): Increased dosage may be required to achieve therapeutic effect.

Specifically, β-receptors exhibit diminished responses to both agonists and

antagonists; e.g. a 65-year-old requires 5 times the dose of isoproterenol needed by a 25-year-old to increase the heart rate by 25 beats/minute. Similarly, greater concentrations of propranolol are necessary for the same level of β-blockade in the elderly (70).

Adverse Drug Reactions

Generally, adverse drug reactions (ADRs) are categorized as allergic (e.g. penicillin rash), nonallergic (e.g. methyldopa-induced hemolysis), and idiosyncratic (e.g. chloramphenicol-caused aplastic anemia). ADRs are more prevalent in the elderly because of their greater use of drugs, (i.e. polypharmacy) and the consequences of ADRs may be more severe (160–163).

The risk factors for ADRs are age, gender, race (occurring most frequently in elderly white women), number of drugs, dosage, duration of treatment, patient overcompliance (e.g. excessive dosage), and underlying conditions (e.g. hepatic or renal insufficiency) (161, 164).

Three significant risk factors relate to age, gender, and prescribing patterns. Caranasos et al. (163) found that the incidence of adverse drug reactions was substantially higher in a group of patients between ages 61–80, but even greater in the 71–80 year old group. These individuals were hospitalized for ADRs, were more seriously ill, and were confined for a longer period than groups of younger individuals. Schimmel (165) found that once hospitalized, elderly patients were more susceptible to drug effects. Smidt & McQueen (166) found that not only were adverse reactions and frequency greater between 60–75 years, but that the percentage of ADRs in the hospitalized patients older than age 60 was 5.6%, in contrast to 1.6% in a group less than age 30.

For unknown and perplexing reasons, women older than age 65 appear to be more susceptible to ADRs. This finding may be associated with greater drug usage in elderly women (160, 163, 167, 168). Jick et al (159) have reported that elderly women appear to be more susceptible to bleeding problems as a result of heparin administration, and the Boston Collaborative Drug Surveillance Program (169) has shown a greater incidence of mental depression from benzodiazepine use in women. Although Greenblatt et al (170) and Allen et al (171) have shown a reduced clearance and longer half-life for benzodiazepines in elderly men, the adverse reactions to this class of drugs in women may result from a greater volume of distribution owing to an increased fat depot for this lipophilic compound.

Drug use should be predicated on the presence of disease. The frequency of

common chronic conditions in persons greater than age 65, in decreasing order of frequency are arthritis, hypertension, hearing impairment, heart disease, visual impairment, and diabetes mellitus. Historically, Jick (172) has shown that the most frequently prescribed medications in an elderly population are furosemide, hydrochlorothiazide, potassium chloride, lidocaine, digoxin, and quinidine. In two reports (168, 172), based on patients over age 65, 77–87% of patients studied received drugs. Stewart & Cluff (168) found that as many as 14 drugs were given at one time per patient. One survey of older residents in an urban apartment building found that the average number of prescription drugs per individual was 4.5. The average number of over-the-counter drugs, not considered drugs by patients, was 3.4 per individual. The sum of 7.9 per person is a truer reflection of the number of medications taken by the elderly on an outpatient basis.

Hospitalized elderly receive more drugs than elderly in an ambulatory care setting (177, 178). The 4.5 number reported above is increased to nearly 6 while in hospital (179). This number may reflect the acuteness of the problem, however, and may be justifiable. Nonetheless, changes in drug regimen toward a lower number of medications at discharge does not necessarily occur. To make matters worse, patients in long-term facilities, i.e. nursing homes, are given between 7–8 or more drugs per day. Why drug interactions are said to occur with greater frequency in nursing home patients is understandable (173–176). The most commonly prescribed medications in nursing homes include haloperidol, thioridazine, digoxin, and furosemide. It can readily be understood why arrhythmias as a result of hypokalemia and conduction defects may be more common in nursing home patients as a result of some of these medications.

Multiple studies have confirmed the overusage of psychotropic drugs in the elderly (180, 181). These drugs include sedatives, hypnotics, tricyclic antidepressants, benzodiazepines, phenothiazines, and butyrophenones (182). Often these drugs are given for nonpsychiatric disorders. Zawadski et al (183) and Thompson et al (180), found the use of psychotropic drugs to be greater in institutionalized elderly than in corresponding groups living in the community.

Regardless of whether the drug use is outpatient, inpatient, or in an extended care facility, drugs whose therapeutic index is low need to be given in reduced dosage and at a longer dosing interval. By adhering to this basic principle, the incidence of adverse reactions involving cognition, drowsiness, gait disturbances, and falls as a result of benzodiazepines, tricyclic antidepressants, or major tranquilizers could be reduced.

A thorough pretreatment history may reveal symptoms that might otherwise be attributed incorrectly to a drug prescribed later (184–186). The history is critical in differentiating possible ADRs from underlying disease. A symptom appearing 1 to 2 months after a medication regimen has been started

Table 11 Clinical presentations of adverse drug reactions (ADRs) in the elderly[a,b]

Restlessness
Falls
Depression
Confusion
Loss of memory
Constipation
Incontinence
Extrapyramidal syndromes (e.g. parkinsonism, akathisia, tardive dyskinesia)

[a] These are also manifestations of various organic illnesses in the elderly.
[b] Adapted from Ref. 187.

may indicate a new (or previously dormant) disease process rather than an ADR.

Elderly patients may develop ADRs that are clearly different in their manifestations from those seen in younger patients (185). Sudden changes in cognition and bowel and bladder continence, mobility disturbances such as falls, and decreased food intake resulting in weight loss may be manifestations of silent myocardial infarction, sepsis, but also of adverse drug reactions. Some of these clinical presentations that could be due to disease or drug reactions are listed in Table 11.

The decision to administer a drug must take into consideration the potential benefits and risks to the patient. A serious ventricular arrhythmia due to psychotropics raises the question as to why the psychotropic drug is being given, but the arrhythmia must be treated despite the potential toxicity of antiarrhythmic agents (26). The benefits incurred by reducing systolic and diastolic elevations in blood pressure and preventing stroke or heart failure usually outweigh the risks of ADRs associated with many antihypertensive agents (188), but the special needs of the patient (diabetes mellitus, bronchospastic disorders) should be considered in selection of therapy.

In summary, the drugs most commonly associated with ADRs (154) in the

Table 12 Adverse drug reactions (ADRs) and source of care administration[a]

Hospital-acquired	Home-acquired
Digoxin	Tranquilizers (phenothiazines)
Aminoglycoside antibiotic	Sedative-hypnotics
Anticoagulants (heparin and warfarin)	Warfarin
Insulin overdose	Antacids
Steroid-induced GI bleeding	Oral hypoglycemics
Aspirin	Digoxin
	Aspirin

[a] Adapted from Refs. 163 and 168.

elderly are analgesics, antibiotics, anticoagulants, antidepressants, antihypertensives, antiparkinsonian drugs, antipsychotics, bronchodilators, digitalis, diuretics, NSAIDs, oral hypoglycemics, and sedative-hypnotics. The distribution of ADRs within these categories varies with the site of care (see Table 12). Because elderly patients may be unable to articulate a complaint, or may suddenly develop gait or balance abnormalities, bowel and bladder dysfunction, or changes in weight, *the family* and/or *physician* must be aware of the drug-induced diseases whose manifestations might erroneously be ascribed to "aging."

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