A REFERENCE TABLE BASED ON AGE RELATED PHYSIOLOGICAL CHANGES AND PHARMACOLOGICAL RESPONSE FOR ASSESSMENT AND MANAGEMENT OF MEDICATION THERAPY IN THE ELDERLY

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ABSTRACT

A REFERENCE TABLE BASED ON AGE RELATED PHYSIOLOGICAL CHANGES AND PHARMACOLOGICAL RESPONSE FOR ASSESSMENT AND MANAGEMENT OF MEDICATION THERAPY IN THE ELDERLY

By

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Medication therapy and education are one of the most important services that Advanced Practice Nurses provide in a primary care or long-term care setting for elderly clients. Inappropriate medication therapy may cause adverse effects such as drug toxicity or lack of drug efficacy as a result of incomplete understanding of changes in the pharmacokinetic processes of drug disposition with aging.

This project examines how some age-related physiologic factors alter pharmacologic response and therefore drug management in elderly clients. The specific factors that were investigated in the project include: 1) renal function, 2) hepatic function, 3) body composition, 4) baroreflex function, and 5) protein binding.

In order to assist Advanced Practice Nurses with more assurance and competency in drug management, a drug reference table was developed. The Reference Table contains some of the significant physiological changes and pharmacological responses that occur with aging. Strategies to prevent drug toxicity and inappropriate medication therapy are also included.

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INTRODUCTION

Elderly individuals in the United States represent the fastest growing segment of the population and are the largest consumers of both prescription and over the counter medications. The most significant reasons for this consumption are the increased number of elderly and the prevalence of chronic diseases such as cardiovascular, arthritis, diabetes, and psychosomatic disorders with advancing age. In considering the most comprehensive management of chronic diseases with medication usage among elderly, it is essential to be aware of the physiological changes that occur with normal aging. The purpose of this project was to develop a reference table that can be utilized by Advanced Practice Nurses (APNs) and the other health care providers in determining what specific age-related physiological factors need to be considered in relation to medication therapy in elderly clients.

With aging there are many changes that occur. Klein, German, and Levine (1981) identified decrease in total body water and lean body mass, baroreceptor sensitivity changes, renal blood flow and glomerular filtration rate changes, liver mass and enzyme activity and the protein binding ability of drugs as the most significant changes.

Drug toxicity in the elderly can be related to these biologic factors, but can also occur through the process of pharmacokinetics and pharmacodynamics. Pharmacokinetics, the study of the action of drugs within the body, deals with route, mechanisms of absorption and excretion, rate at which a drugs action begins, duration of the effect, biotransformation of the substance in the body, and effects and routes of excretion of the metabolites of the drugs (Bourne, 1995). Pharmacodynamics is the study of how a drug acts on a living organism, including the pharmacologic response observed relative to the concentration of the drug at an active site in the organism (Bourne, 1995). Understanding these two factors in relation to age-related physiological changes helps to predict or monitor the adverse drug reactions that are common in elderly.

The findings of numerous research studies can be found in the literature documenting the difficulties elderly individuals encounter with medications. According to studies from the Boston Collaborative Drug Surveillance Program (1973, 1977 & 1978), there is a clear relationship between age and associated untoward responses to benzodiazepine derivatives such as chlordiazepoxide, diazepam, fluazepam, and nitrazepam (Greenblatt, Sellers, & Shader, 1982). The study by Cook, Flanagan, and James (1984) found that an average dose of diazepam needed to produce the same degree of sedation for 80 year old clients was 10 mg, whereas the dose for 20 year old clients was 30

mg. The researchers concluded the difference of neurological response to diazepam may be related to pharmacodynamic changes that occur with aging. Castleden, George, Marcer, and Hallett (1977) reported that increased sensitivity to nitrazapam in old age is due to a change in the aging brain rather than a change in pharmacokinetics.

For the cardiac agents lidocaine and propranolol, a relatively weak association of age to clinical toxicity has been reported. Digoxin is one of the most widely prescribed cardiogenic drugs and is believed to be used throughout the life span after it is first prescribed. Digoxin is however, responsible for over 20% of all adverse drug reactions occurring in hospital in-patients; one third of these being life-threatening (Cusack, Kelly, O'Malley, Noel, Lavan, & Horgan, 1979). The rate of absorption, determined by the time of peak concentration after an oral dose, was more rapid with young patients than the old. Although the extent of absorption was similar in both the young and old groups, mean plasma half-life was longer in elderly patients. Looking at drug distribution, the absolute apparent volume of distribution was reduced in the older patients and correlated inversely with age. The study also found that digoxin appears to be mainly distributed in the lean body mass compartment, which is reduced in old age. The most significant finding of the study is that of an association between an elevated plasma level of digoxin and decreased renal function commensurate with age.

Adverse drug reactions may be difficult to distinguish from disease symptoms, particularly among the elderly in whom identification of adverse drug effects is complicated by the existence of multiple concurrent diseases and consumption of a disproportionate amount of drugs (Nolan & O'Malley, 1988). Thus, these reactions are easily dismissed as signs of aging or symptoms of disease processes. In addition, Basen (1977) lists the following barriers to appropriate management of adverse drug effects in the elderly. First, there is little systematic research on specific adverse effects during chronic drug therapy, since most toxicity studies are based on single dose or short-term dosing. Second, there is a lack of studies about the characteristics of those at highest risk for drug effects. Finally, there is an insufficient understanding on the relationship between multiple drug therapies and incidence and severity of adverse drug effects.

Greenblatt, Sellers, and Shader (1982) claim that most of the current scientific understanding of therapeutics, clinical pharmacology, and pharmacokinetics is based on studies in young people. Additionally, the approach to therapeutics in elderly clients is frequently based on anecdotal data, clinical impression, and trial and error.

PURPOSE

The effects of inappropriate medication use can be complicated and often life threatening. Numerous studies document the evidence of inadequate prescribing, inadequate

supervision, and lack of communication between elderly individuals and health care providers. Few studies document the relationship between the normal process of aging, alterations in physiology and functional capacity, and age-related changes in pharmacodynamics and pharmacokinetics. Yet, major complications and adverse effects result because of either a lack of understanding on the prescriber's part regarding geriatric pharmacotherapeutic management, or not taking age-related changes into consideration when prescribing medications. Therefore, learning pertinent information leading to the pharmacological response to age-related physiological changes and appropriate management should give both APN's and their clients maximum safety in medication therapy. This project focuses on drug management guided by age-related physiological changes and pharmacological response. The purpose of this scholarly project was to develop a reference table that can be used by the APN in determining what specific age-related physiologic factors need to be considered before prescribing medications to elderly clients. The specific age-related physiologic factors addressed are: 1) renal function, 2)hepatic function, 3) body composition, 4) baroreceptor function, and 5) protein binding.

REVIEW OF LITERATURE

Although no two people age at the same rate, the efficiency of the human body declines gradually with age. For example, the average seventy-five year old has 92

percent of his/her brain weight at age thirty, 84 percent of the metabolic rate, 70 percent of the kidney-function rate, and 43 percent of the breathing capacity (Leaf, 1973). These changes in organ and tissue function may alter responsiveness to drugs, which can result in the development of unpredictable effects of pharmacotherapy in elderly clients. The following list summarizes some age-related physiologic changes and altered drug responses as a consequence of these changes (Staab, 1996; Troncale, 1996).

It is believed that pharmacodynamic changes in the elderly may be due to changes in receptor affinity or number or to changes in hormonal levels (Pagliaro & Pagliaro, 1983; Roberts & Tumer, 1988). Reidenberg, Levy, Warren, Coutinho, Schwartz, Yu, and Cheripko (1978) demonstrated that elderly clients are sedated with a lower serum concentration of diazepam than is required for younger ones. Another example of pharmacodynamic change with aging is the decreased requirement for thyroid hormone in elderly hypothyroid clients (Davis, LaMartia, Spaulding, Wehman, & Davis, 1984; Swan, Herman, Molitch, Londen, & Kramer, 1983).

Another evidence of pharmacodynamic action and receptor sensitivity related to aging is found in the combined use of amino glycosides and ethacrynic acid which produce hearing loss in the aged even at doses that are well below the toxic doses of each used alone (Roberts & Tumer, 1988). Other drugs that produce ototoxicity, such as aspirin, nonsteroidal anti-inflammatory agents, vancomycin

List 1.

Age-related Physiologic Changes and Consequent Altered Drug Response [Adopted from Staab (1996) & Troncale (1996)]

AGE-RELATED CHANGES	ALTERED DRUG RESPONSE
Reduced gastric acid increased PH (less acid)	Rate of drug absorption may be delayed
Reduced GI motility	Extent of absorption not affected
Prolonged gastric emptying	
Decreased albumin sites	Significant changes in protein binding, leading to a higher level of unbound drug; therefore, more effect and faster metabolism and excretion
Decreased lean body mass	Higher lean drug levels
Increased percentage of body fat	Fat-soluable drugs remain in system longer
Reduced body water	Water soluable drugs have smaller volume of distribution
Decreased hepatic function Decreased perfusion of the liver	Decreased metabolism and delayed breakdown of drugs, leading to extended duration of action, accumulation, and toxicity
Decreased Glomerular Filtration Rate (GFR)	Poor renal excretion of drugs
Decreased renal blood flow Loss of functioning nephrons	Increased danger of accumulation and toxicity

(vansocin), and quinidine, are more likely to produce ototoxicity in elderly persons apart from changes related to pharmacokinetics (Roberts & Tumer, 1988). Some examples of age-related alterations in drug sensitivity are reported in the following list.

List 2.

Examples of Age-Related Alterations in Drug Sensitivity

Cardiovascular
propranolol (decreased)
verapamil (decreased)
furosemide (decreased)
theophylline (increased)

Central Nervous System
benzodiazepines (increased)
halothane (increased)
narcotic nalgesics (increased)
metoclopramide (increased)

Endocrine
insulin sensitivity (decreased)
cortisol suppression (decreased)

Immune/Antihistamine
antibody response to vaccination (decreased)

Respiratory
theophylline (decreased)

Anticoagulants
warfarin (increased)

In 1994, a panel of judges which consisted of 13 geriatricians and pharmacists from the United States and Canada, investigated inappropriate drug use in community-residing older persons (Lee, 1996; Stuck, et al. 1994). The following list is a compilation of the medications that should be avoided for elderly individuals. Lee (1996) and Stuck et al. (1994) found that dose, duration of therapy or clinical circumstances were not significant enough reasons in using these specific medications for the elderly.

List 3.

Medications to be Avoided in Elderly Individuals Regardless of Dose, Duration of Therapy, or Clinical Circumstances

MEDICATION CLASS	REASON/PROBLEM
Sedative or Hypnotic Agents	
Long-acting Benzodiazapines	Produce daytime hangover-like effect due to prolonged duration of action
diazepam (Valium)	
chlordiazepoxide (Librium)	
flurazepam (Dalmane)	
Meprobamate (Equanil, Miltown)	Accumulates with repeated dosing
Short-duration Barbiturates	Short-acting benzodiazapines are safer alternative
pentobarbital (Nembutal)	
secorbarbital (Seconal)	
Antidepressants	Has potent anticholinergic side effect
amitrypline (Elavil)	
Combination Antidepressants/ Antipsychotics	Other antidepressant medications have less anti-cholinergic side effects
Nonsteroidal Anti-inflammatory Drugs	
Indomethacin (Indocin)	Headaches are more common May worsen depression
Phenylbutazone (Butazolidin)	Other NSAIDs cause less toxic reactions (Indomethacin-CNS, phenylbutazone-hematologic)
Oral Hypoglycemic Agents	
chlorpropamide (Diabenese)	Cause prolonged hypoglycemia Other oral hypoglycemic medications have shorter half-lives
Analgesic Agents	
propoxyphene (Darvon)	Metabolite, norpropoxyphene, can cause arrhythmias, particularly in patients with impaired renal function
pentazocine (Talwin)	Can cause seizures, hallucinations, or arrhythmias when taken in large doses

MEDICATION CLASS	REASON/PROBLEM
Dementia Treatments	
cyclandelate (Cyclospasmol) (Note: cyclandelate is no longer available in the U.S.)	Effectiveness is in doubt
Isoxsuprine (Vasodilan)	
Antihypertensive Agents	
reserpine (Serpalan)	Other antihypertensive medications cause fewer side effects such as depression and sedation
Platelet inhibitors	
dipridamole (Persantine)	Effectiveness at low doses is in doubt, toxic reaction (orthostatic hypertension) at higher doses Aspirin is safer alternative
Muscle Relaxants	
carisoprodol (Soma) cyclobenzaprine (Flexeril) methocarbamol (Robaxin) orphenidrate (Norflex)	Potential for CNS toxicity is greater than potential benefit
Gastrointestinal Antispasmodic Agents	
belladonna (Donnatal) clidinium (Librax) dicyclomine (Bentyl) hyoscyamine (Anaspaz)	Minimally effective while causing toxicity, including sedation and anticholinergic side effects
Antiemetic Agents	
trimethobenzamide (Tigan)	Least effective of the available antiemetics

The incidence of high usage and serious side effects of psychotropic drugs among elderly have been thoroughly documented (Cadieux, 1993; Richelson, 1984; Spore, Mor, Larat, & Hawes, 1995; Thompson, Moran, & Niles, 1983). Many older individuals believe their daily performance depends on the use of such drugs. Unfortunately, most of these

psychotropics are fat-soluble, and have an extended half-life. Further, because the lean body mass decreases and the total body fat increases, the total body water decreases with aging, water-soluble agents, including alcohol and lithium carbonate, become more concentrated, and thus more potent (Cadieux, 1993).

Although there are only a few studies that convincingly demonstrate a true change in drug sensitivity in old age, it is still an important consideration when drug actions are examined for their added or decreased effect, since the effect may range from subtherapeutic to major toxicity. Greenblatt et al. (1982) noted that many pharmacokinetic changes occurring in the elderly are logical consequences of age-related changes in body composition and organ-system function. In addition, protein binding and baroreflex function must be considered with drug therapy.

Renal Function

The major effect of aging on pharmacokinetics is reflected in drug clearance (German & Burton, 1989). Clearance is the best indicator to describe the ability of the body to remove drugs. Clearance is also the best measure to determine the extent of drug accumulation during multiple drug usage. As a person ages, there is a decline of about 35% in glomerular filtration rate. The total clearance of the drug by the kidneys will decline in proportion to the reduced glomerular filtration rate (Rowe, Andres, Tobin, Norris, & Shock, 1976). Renal function

steadily decreases with age, affecting the excretion and clearance of drugs. This reduction in renal function and drug clearance can be accurately measured by available clinical tests, thus giving health care providers a clear picture as to how at-risk the client will be with certain drug dosing regimens. Drugs such as amino glycoside antibiotics rely totally on the kidneys for excretion and would be expected to have the clearances reduced proportionally with change in renal function (Lee, 1996; Yuen, 1990).

Laboratory tests needed to diagnose impaired renal function are serum creatinine and Blood Urea Nitrogen (BUN) levels. Creatinine is the by-product of muscle energy metabolism and is produced at a constant rate, depending on the muscle mass of the person and is removed from the body by the kidneys primarily through glomerular filtration (Fischbach, 1992). The normal value of creatinine for an adult is 0.6-1.2 mg/dL. An elevated BUN is seen with rapid protein catabolism and impaired kidney function. Although BUN alone is less sensitive in predicting kidney impairment than when it is viewed together with the creatinine level, it is still a good indicator when viewed alone for chronic renal failure. Normal range for an adult is 7-18 mg/dL (Fischbach, 1992). A BUN of 50-150 mg/dL indicates serious impairment of renal function in the elderly.

The normal creatinine clearance level for healthy young adults is 100-120 mL/minute. After age 40, creatinine

clearance falls by 10% for every decade of life. A 70 year old will typically have a creatinine clearance of about 70 mL/minute (Lee, 1996). Although creatinine is co-ordered with virtually every quantitative urine test, formulas calculating creatinine clearance levels in men and women are provided below. If calculations indicate that a client has below-normal renal function, the pharmacological dosing regimen should be adjusted.

Formulas to calculate Creatinine Clearance:

For Men: Creatinine clearance(mL/minute)=

$$\frac{(140\text{-age}) \times \text{weight (kg)}}{(\text{serum creatinine (mg/dL)} \times 72)}$$

For Women: Creatinine clearance (mL/minute)=

$$\frac{(140\text{-age}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72 \times 0.85}$$

The following list of medication is commonly associated with dosage adjustment based on diminished renal function. This list is based on the work of Lee (1996).

Hepatic Function

The incidence of excessive accumulation of such drugs as digoxin, cimetidine, lithium, procainamide, chloropropamide, and common antimicrobial agents with aging is contributed to the effect of physiological change. Long-acting benzodiazepines and cimetidine can be a particular risky combination in older individuals, as cimetidine inhibitis the hepatic microsomal enzymes that break down long-acting benzodiazepines. The drugs duration of action

List 4.

Common Medications Requiring Dosage Adjustment Based on Diminished Renal Function

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allopurinol (zyloprim)
Amino Glycosides:
 amikacin (Amikin)
 gentamicin (Garamycin)
 netilmicin (Netromycin)
 tobramycin (Nebcin)
atenolol (Tenormin)
chlorpropamide (Diabenese)
cisplantin (Platinol)
digoxin (Lanoxin)
Histaminie-2 Receptor Antagonists:
 cimetidine (Tagamet)
 famotidine (Pepcid)
 nizatidine (Axid)
 ranitidine (Zantac)
 nitrofurantoin (Furadantin)
 plicamycin (Mithracin)
 sulfonamides, such as trimethoprim-sulfamethoxazole
 (Bactrim, Septra)
lidocain (Xylocaine)
lithium carbonate (Eskalith, Lithobid, Lithotab)
methotrexate (Folex)
nadolol (Cogard)
vancomycin (Vancosin)

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is prolonged and increased accumulation can lead to oversedation, confusion, or ataxia (Lee, 1996). Cusson (1985) found a significant correlation between lidocaine clearance and age in 35 patients with suspected myocardial infarction ages 35 to 91 years. The researchers found that as age increased, lidocaine elimination decreased.

Flow-dependent drugs exhibit `first pass' effect in which a drug enters the portal circulation after absorption from the gut before reaching systemic circulation. In the elderly, who have reduced liver blood flow, the first pass

effect is lessened, so that more drug can reach systemic circulation (Yuen, 1990).

With aging, the size of the liver decreases by 24-35%, even when body mass is taken into account (Woodhouse & Wynne, 1988). The liver blood flow also decreases by over 35% between young adulthood and senescence in humans (Woodhouse & Wynne, 1988).

The hepatic clearance of a drug is probably reduced by decreased liver size and decreased liver blood flow in the elderly. Although the liver is the major organ involved in metabolism of drugs, clinical lab tests for liver function do not correlate well with the liver's ability to metabolize drugs (Yuen, 1990). Various medical conditions and drugs that directly or indirectly impair liver function need to be monitored closely for significant accumulation and possible drug toxicity. The following list illustrates certain medical conditions and drugs that impair liver metabolism (Lee, 1996).

Protein Binding

Plasma protein binding affects body distribution of drugs. Albumin makes up more than half of the total serum protein; it is the principal circulating protein to which drugs bind (Lee, 1996). Decline of albumin production is thought to be associated with age-related changes in the liver such as liver size, blood flow, and enzyme production (Goldman, 1986). The normal range for albumin in young adults is 3.2-4.5g/dL. It is 2.3-4.7g/100mL in older males

List 5.

Causes of Impaired Hepatic Metabolism

CONDITIONS	DRUGS
cirrhosis	allopurinal (Zyloprim)
liver cancer	cimetidine (Tagamet)
heart failure	ciprofloxacin (Cipro)
fever	diltiazem (Cardizem)
malnutrition	enoxacin (Penetrex)
thyroid disease	erythromycin
	fluconazole (Diflucan)
	isoniazid (Nydrazid)
	ketoconazole (Nizoral)
	metronidazole (Flagyl)
	ranitidine (Zantac)
	trimethoprim-sulfamethoxazole (Bactrim, Septra)
	verapamil (Calan, Isoptin)

and 2.6-5.9g/100 mL in older females (Kain et al., 1990). Once drugs are absorbed and enter the circulation, many drugs bind to proteins. The following list of drugs are an example of highly protein bound drugs (see List 6).

With reduced concentration of albumin in the elderly, drugs that are highly bound to albumin will have an increased amount of unbound or free fraction of drug available in the blood stream. This would result in a larger volume of distribution as more drug is free to distribute to the rest of the body (Yuen, 1990). Although this alteration in distribution and protein binding alone may not be clinically significant (Lee, 1996; Woodhouse, 1988), when the individual has an illness or a medical condition that reduces drug binding to albumin, higher

List 6.

Highly Protein Bound Drugs

Oral Anticoagulants	warfarin (Coumadin) aspirin
Oral Hypoglycemics	tolbutamide (Orinase)
Calcium Channel Blockers	verapamil (Calan)
Loop Diuretic	furosemide (Lasix)
Nonsteroidal Anti-Inflammatory Drugs	diflunisal (Dolobid) naproxen (Naprosyn, Anaprox)
Anticonvulsants	phenytoin (Dilantin) valproate (Depakene)
Antidysrhythmic	quinidine (Quinalan)
H^2 Histamine Blocker	cimetidine (Tagamet)

concentrations of free fraction may bring about lower therapeutic levels and greater risk of toxicity. Warfarin is known to cause such toxic effects because it is 99% protein bound (Lee, 1996). Thus, any increase in the unbound fraction can raise the risk of excessive anticoagulation and bleeding complications. Older clients who have conditions known to reduce albumin serum concentration or drug binding to albumin warrant close observation for warfarin toxicity (Lee, 1996). Decreased serum albumin is present in such conditions as diarrhea, malnutrition, immune disorders, and metastatic cancer. It

may also be a sign of chronic infection or nephrotic syndrome (Staab & Hodges, 1996).

Body Composition

The alteration in body composition with age influences distribution of drugs. In aging from 25 years to 75 years old, fat content increases from 15% of body weight to 30% of body weight, tissue (fat free mass) decreases from 17% to 12%, and intracellular water decreases fro 42% to 33% (Rossmann, 1979). Minor changes occur in body weight across the adult life span and major redistribution of tissue proportions also occur.

Parallel to the age changes in fat and fat free mass proportions, Total Body Water (TBW) which consists of Intracellular Fluid (ICF) and Extracellular Fluid (ECF) is found to be changing with increasing age. Greenblatt (1982) concludes that the effect of age-related changes in body composition on body drug distribution depends largely on the drug's aqueous and lipid solubility. Some drugs, such as acetamenophen, antipyrine, and ethanol, are relatively water soluble and lipid insoluble, and they would be expected to have a lower volume of distribution as the percentage of body water is decreased. Conversely, more lipid-soluble drugs, such as diazepam and lidocaine would be expected to have a larger volume of distribution in elderly as the percentage of body fat is increased.

Baroreflex Function

Unlike the four previously discussed age-related physiologic parameters which primarily affect pharmacokinetics, blunting of baroreflex function is manifested by mechanisms of pharmacodynamics. Pharmacodynamics, as previously defined, deals with the type, intensity, and duration of effect of a given concentration of a drug at the site of action (Woodhouse & Wynne, 1992). With advancing age, the baroreceptors, located in the carotid sinus and elsewhere, become less sensitive and result in a postural hypotension response to many drugs such as antihypertensive agents, neuroleptics, tricyclics, benzodiazepines, and antiparkinsonian drugs (Woodhouse & Wynne, 1992). Feely and Coekley (1990) point out that the elderly individual who takes alpha-adrenergic blockers or potent diuretics are at particular risk because of this loss of efficiency of homeostatic response.

Explanations of how the mechanism of baroreflex bluntin occurs varies from one author to another. Pagliaro and Pagliaro (1983), and Roberts and Tumer (1988) report that age differences in responsiveness may be due, in part, to alterations in receptor number or affinity. According to Gribbin, Pickering, Sleight, and Peto (1971), decreased sensitivity of the baroreflex may be partly a function of reduced arterial distensibility. While observing the blunted cardiovascular response to the stress of exercise, Yin (1980) concludes that with advancing age, the smooth

muscle of the walls of the arteries becomes less responsive to beta-adrenergic stimulation and to other vasoactive hormones. The following list summarizes drugs that commonly cause postural hypotension in the elderly (Wollner & Collins, 1992).

List 7.

Drugs Commonly Used in the Elderly Which Can Cause Postural Hypotension

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Thiazide and loop diuretics
Phenothiazines
Tricyclic antidepressants
Butyrophenones
Benzodiazepines
Levodopa
Bromocriptine
Barbiturates
Antihistamines
Glyceryl trinitrate
Vasodiator hypotensive agents
Adrenergic beta-blocking agents
Insulin
Alcohol

Understanding both age-related physiological changes and pharmacological responses in the elderly is especially important in helping to design more effective and less toxic drug dosage schedules for older individuals who need to begin pharmacologic agents, and or whose medication schedules is already established. Sheahan, Hendricks, and Coons (1989) reported that 82% of older adults who live independently use over-the-counter medications. This excessive use of over-the-counter drugs by elderly is reinforced by the advertisement prone attitude, thinking

that "there is a pill for every ill." Bliss (1981) reported up to 50% of clients expect a visit with a physician to result in the prescription of a drug. To make matters worse, many physicians believe that patients expect a prescription even when the patient does not expect one (Montamat & Cusack, 1992).

In summary, while theories of aging try to explain how the body and mind change with age, we know there is a progressive decline in physiologic functioning. The implication of functional decline in organs with aging is increasingly important in regard to drug therapy. The problem is no research was found that linked the normal physiological changes with specific pharmacological response. The purpose of this scholarly project was to develop such a reference table and was accomplished by utilization of the concepts that follow.

CONCEPTUAL DEFINITIONS

For purposes of this scholarly project the terms pharmacodynamics, pharmacokinetics, and age-related changes are defined. **Pharmacodynamics** is the study of the biochemical and physiological effects of drugs and their mechanisms of action and the effect of drugs at the target site (such as how a receptor governs the type, intensity, and duration of drug action) or simply stated, how a drug acts on a living organism. It has been suggested that major pharmacodynamic changes in the body's response to drugs only become manifested at ages 70 to 75 years or beyond. Studies

on middle-aged or late-middle-aged may not reveal such changes (Roberts & Tumer, 1988).

Pharmacokinetics is the study of the time a drug metabolites when levels can be detected in different bodily fluids during the absorption, distribution, metabolism and elimination phases of the drug. **Age-related Changes** are the changes that occur in any cell or organ system as a function of time, independent of abnormal external or pathologic influences (Staab & Hodges, 1996). Age-related biological changes include diminished number of cells in most body tissues, changes in metabolism, permeability and respiration, proliferation of connective and fat tissues, impaired adaptation to stress, decline in muscle strength and oxygen use, and sensory perception (Malseed, Goldstein & Balkon, 1995).

Psychosocial changes related to aging occur in a host of directions and affect significantly the quality of life of an older individual. However, the age-related psychosocial changes in regard to medication therapy were beyond the scope of this project.

THEORETICAL FRAMEWORK

Aging is a part of the normal life cycle. Physiological changes occur in humans as internal and external stresses impinge upon normal states by altering the homeostatic environment. Pender (1987) believes that these age-related changes can be delayed or minimized through a healthful life style. Pender advocates health protecting

and health promoting activities be maintained throughout the total life span, from infancy-childhood to the older adult years.

Pender (1987) describes prevention as a "defensive posture" or "set of actions" that ward of specific illness conditions or their sequelae and threaten the quality of life or longevity. Pender (1987) further defines health protection as an action directed toward "decreasing" the probability of experiencing illness by active protection of the body against pathological stressors or detection of illness in the asymptomatic stage. Health promotion, in which Pender's theory has become better known, is directed toward" increasing "the level of well-being and self-actualization of a given individual or group.

The incidence of major complications and adverse effects from inappropriate medication therapy is preventable. There is an increased awareness among the general public, as well as health care providers, to be cautious about the potential risks for adverse drug reactions, whether drugs are taken by the consumers or prescribed by the health care providers. This project focused on the issue of protecting clients from potential complications and adverse drug events by decreasing the probability of inappropriate prescribing. Understanding a drug's pharmacokinetic and pharmacodynamic processes helps the APN protect clients from preventable adverse drug events.

Following Pender's proactive definition of prevention, merely understanding pharmacological responses or a person's physiological changes will not be enough guarding against adverse drug events. APN's must prescribe defensively and must evaluate clients critically for physiological changes that would impact their response to medications.

The Model for Medication Therapy (Figure 1) examines how an older individual and APN's can work together to achieve higher quality of life while increasing years of life on earth. It is obvious that the goal of preventing undesired effects, caused by inappropriate medication therapy, and the goal of achieving increased quality of life for people of all ages through health protection and health promotion efforts conceptually coincides.

For elderly individuals who are affected by age-related physical changes, chronic illness, and stressful life events, maintaining a medication regimen becomes even more energy consuming. Every effort should be made to provide non-pharmacological interventions such as rest, diet, exercise, and counseling sessions before pharmacologic agents are used.

APNs should direct their efforts in helping elderly individuals to become more functionally independent through healthy life style strategies such as exercise, smoking and alcohol cessation, proper nutrition, weight control, and

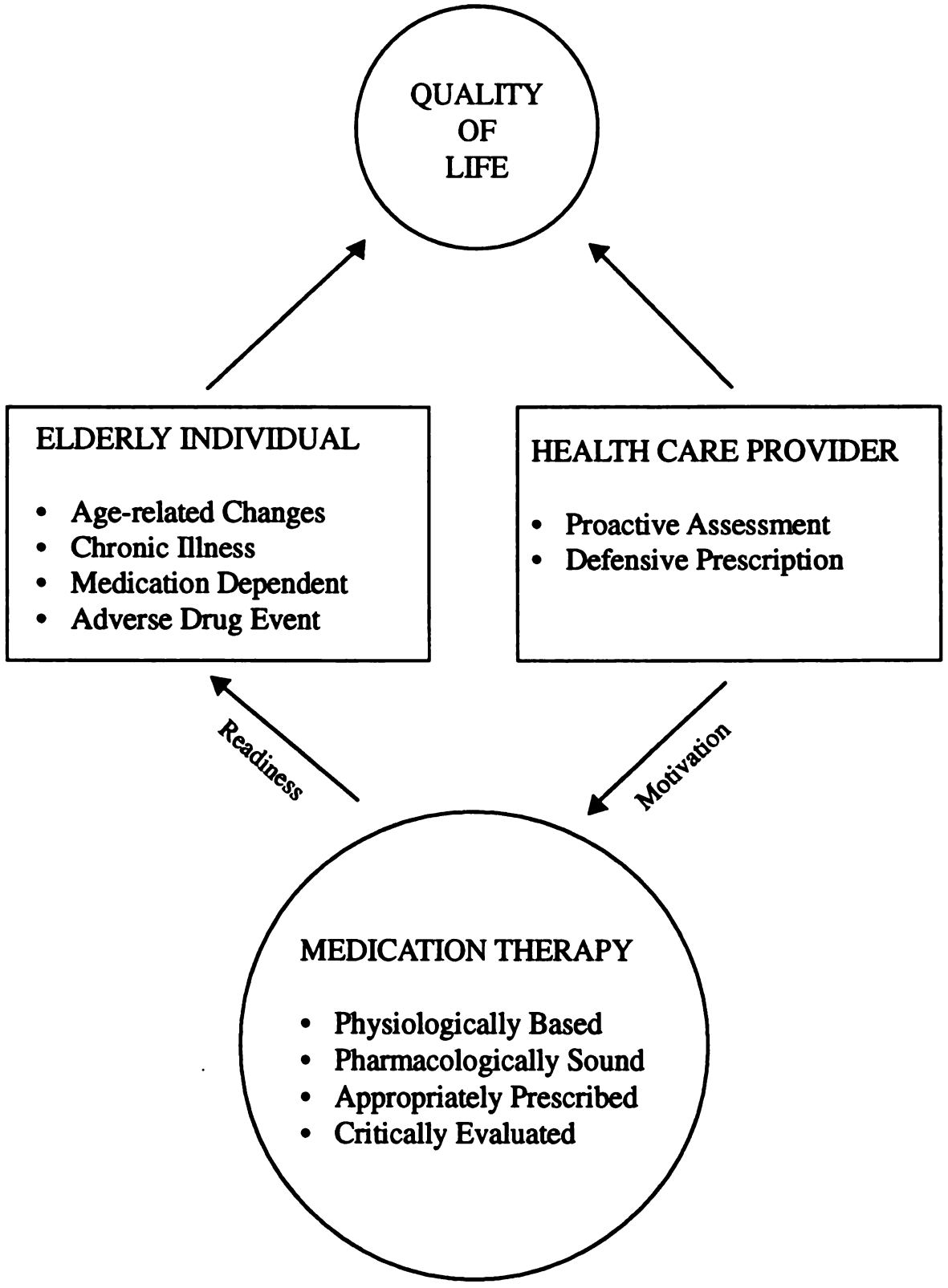

Figure 1. Model for Medication Therapy Based on Health Protection (Pender, 1987).

stress management. The optimal level of functional independence and a positive state of well-being can be accomplished by facilitating health-protecting and health promoting behaviors of elderly individuals. The steps developed in Pender's Model guides APN's to be motivated toward making a difference in prescribing practices. Such a difference could mean either looking for an alternative to drug therapy or assessing the readiness of the client in developing a health protection plan.

Despite the irrefutable merit of Pender's motivational behavior change theory, there are a few limitations in applying the model exclusively to this project. For example, the concepts of motivation, readiness, and changes of behavior are usually directed toward the client rather than the provider himself/herself as implicated in this project. Also, the strategies suggested to promote health and to prevent illness as part of the implementation phase in the model are largely applicable to clients who are receiving care, rather than the provider who provides services.

PROJECT DEVELOPMENT

Although there are many drug references that help APN's and other health care providers with drug therapy, this project focuses specifically on the effect of aging which determines careful selection and monitoring of medication in the elderly population. The Reference table (Appendix) lists major organ systems, pertinent physiological changes

that occur with aging, medications that are commonly prescribed for maladaptive functions of each organ system, and finally the appropriateness of drug management along with it's response to conditions of aging. In order to maximize the use of the table, APN's must first thoroughly review the materials and assess the appropriateness of the prescriptions, while paying special attention to the pharmacokinetic and pharmacodynamic responses of each medication. Only when the appropriate prescription, followed by meticulous monitoring and evaluation is achieved, will the goal of this project, "elderly client protection," be met.

EVALUATION OF PROJECT

Evaluation of this project could be achieved by examining the effectiveness of using the table. One way of accomplishing this would be by evaluating client outcomes in terms of the number of reports of adverse drug incidents, length of stay and number of hospital readmissions, and level of difficulty related to medication management.

Another method to measure the usefulness of the table is to monitor the use of the table by staff. The reports of such use can be tabulated by sending out feedback request forms to clinical sites where the table is currently in use. Costs of using the table should be monitored by considering both the calculation of costs for providing copies of the table and determination of provider time involved using the table.

IMPLICATIONS FOR ADVANCED PRACTICE NURSING IN PRIMARY CARE

Prescribing medication is one of the important services that APN's provide daily in primary or long-term care settings. The focus of this project was to develop a Reference Table that could be used to review and learn important information before prescribing medications for elderly clients in order to provide this service safely and competently.

The Reference Table contains important age-related physiological changes and outlined the pharmacological responses as result of these changes. The table also refers to medications which are significantly affected by aging changes. Since changes in some physiologic parameters with aging, such as renal function, can readily predict changes in drug pharmacokinetics, recognition of the potential impact of these physiological changes with aging should improve the drug prescription practice. The Reference Table can be filed with other drug information or it can be made into a separate chart and laminated. The information can serve as client teaching tools as well as a learning module by putting them into slides or graphic posters.

Medications are and can be of great benefit to the elderly. However, careless prescription practices and inappropriate use of medications on the part of both the provider and the client may result in undesirable outcomes. The risk of these undesirable outcomes may range from a loss of pharmacotherapeutic effect to a life-threatening event.

APNs, now actively seeking prescriptive authority through legislation, must increase their understanding of drug therapy in the elderly. This project may be one of the first steps in that direction.

Although the risk of adverse outcomes in the elderly is compounded by pharmacodynamic and pharmocokinetic changes related to aging, extra time spent on learning the specific effects and particular actions of drugs will greatly improve the client's therapeutic outcomes. Most APNs are not experts in geriatric pharmacology. However when up to 50% of client contacts in primary care settings results in the prescribing of a drug, and since a great portion of clients seen in clinics are elderly, the need for knowledge of geriatric clinical pharmacology is obvious. It is the responsibility of APNs to seek such knowledge.

There has been much public concern expressed over problems with drugs such as Opren (benaxoprofen) and Indocin (indomethacin) because of the serious adverse drug reactions in elderly (O'Malley, 1990). As a result, it is now standard practice by the drug regulatory authorities to require extensive information on pharmacokinetics and pharmacodynamics in the elderly when product authorization is being sought and when used by the elderly is anticipated.

Lamy (1990) states that one of the major reasons for adverse outcomes is poor supervision of chronic care drug therapy. FDA commissioner, Frank Young, states, "central to the problem of adverse drug reactions is inappropriate

prescribing practices by providers." Both statements seem to suggest that there is inadequate knowledge and inadequate monitoring practices. For safe and rational drug therapy in geriatric clients, there must be an increased understanding of the normal aging changes and pharmacology principles.

EDUCATION

The need for knowledge of geriatric clinical pharmacology is obvious for all practitioners who evaluate and treat older clients (Montanat & Cusack, 1992). For preparation in nursing education, introducing a pharmacology course that focuses on the elderly and different ethnic groups at the undergraduate level, may increase the understanding and awareness of nursing students in recognizing adverse drug reactions or toxic effects of medications. The pharmacology course could also incorporate laboratory tests that interpret and predict the safety of certain medications prescribed for older individuals.

At the graduate level of nursing education, it is strongly recommended that the pharmacology texts used must contain drug information that reference the geriatric population. Information on medicating the elderly can also be taught in hospitals and extended care facilities as a form of inservice training and required continuing education. It is hoped that an increase in knowledge information and awareness may generate active discussions on adverse side effects and reactions at community centers for elderly and improve prescriber's practice habits.

RESEARCH

Studies on the effects of aging and provider knowledge on potential problems in the elderly population's drug use are essential if rational drug therapy for the aged is to evolve. Few studies address the special considerations of age in elderly clients (Nolan & O'Mally, 1988; Williamson & Chopin, 1980). A few studies were conducted that investigated effects of adverse drug reaction and physiologic factors that contribute to differences in pharmacotherapeutics (Lee, 1996; Malseed, Goldstein, & Balkon, 1995; Cadieus, 1993; Roberts & Tumer, 1988; Klein, German, & Levine, 1981). The continued investigation of altered drug action based on physiologic changes is needed to determine the proper use of drugs in the elderly. Contrary to the use of drugs, studies addressing nonutilization of pharmacologic agents or alternative treatment plans for illness are strongly encouraged to compare the cost and the outcome of both interventions.

There is also a special need to document perceived client satisfaction related to drug therapy in the elderly. It is important to understand elderly client's perceived quality of life and for this perception to be in line with the provider's drug management strategies. Another research need is related to drug therapy in the elderly. These studies could focus on effective prescribing practice by providers and collaborative practice models among various health disciplines including pharmacists.

CONCLUSION

Martin Green, geriatric consultant in England once stated, "one of the functions of geriatricians is to take off drugs prescribed by other doctors." This statement paints an ironic picture, knowing that medication therapy is an overwhelming expectation by both clients and providers. APN's who are involved in drug treatment must not merely be concerned about relieving client's symptoms or fixing a single organ system, but must be cognizant of the client's overall quality of life as the client perceives it. It is an obligation of APN's to teach, counsel, advocate for and lead the elderly into a healthful course of life.

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APPENDIX A

Age-Related Physiological Changes and Pharmacological Response

System	Age-Related Changes	Commonly Prescribed Medications	Pharmacological Responses
Cardiovascular	• heart size slightly increased or decreased • heart rate decreased • cardiac-output decreased (1%/year after age 30) • stroke volume decreases • longer recovery time after exercise and stress • blunted baroreflex function • decreased beta-receptor sensitivity and plasma renin activity	Digoxin (Lanoxin)	• mainly distributed in lean body mass • low protein binding (20%-30%) • reduced plasma clearance • narrow therapeutic range • monitor closely for toxic effect (normal serum level 0.5-2.0ug/L) • should not be used in acute CHF related to MI
		Ace Inhibitors: Angiotensin converting enzyme captopril (Capoten) enalapril (Vasotec) Lisinopril (Zestril)	• reported not to cause significant reflex tachycardia, due to a resetting of the baroreceptor reflex (1986, British Journal of Clinical Pharmacology, 21, 338) • may cause renal failure due to vasodilation of efferent arteriole in the kidney • caution in clients with a decreased GFR, taking K+ supplements, or K+ sparing diuretics • start with low doses to avoid decreased BP
		Diuretics: furosemide (Lasix) thiazide	• excreted renally, clearance is reduced by 24%-44% in elderly (1990, Clin Geront Med, 6, 276) • may require higher doses due to slower absorption, blunted response, altered sensitivity of renal tubules

System	Age-Related Changes	Commonly Prescribed Medications	Pharmacological Responses
Cardiovascular (cont.)			• clearance is prolonged and plasma levels remain high • monitor electrolytes • watch for postural hypotension, dehydration
		Beta Blockers: propranolol (Inderol) labetolol (Normodyne) atenolol (Tenormin)	• abrupt withdrawals may result in angina, BP (1981, British Heart Journal, 45, 637) • may require increased drug concentration to offset blunted beta-adrenergic effect (1990, Clinics in Gerontological Medicine, 6, 288).
		Calcium Channel Blockers: verapamil (Calan) diltiazem (Cardizem) nifedipine (Procardia) nicardipine (Cardene)	• undergo extensive first-pass hepatic extraction after absorption • metabolized extensively in the liver and none of each drug is excreted unchanged (1992, Medical Gerontology, 4, 133) • increased risk of postural hypotension due to decreased baroreflex activity

System	Age-Related Changes	Commonly Prescribed Medications	Pharmacological Responses
Gastrointest-inal	• decreased production of hydrochloric acid • decreased GI blood flow • decrease in size and permeability of capillary bed • decreased pancreatic trypsin • decreased GI motility and peristalsis • decreased production of pepsinogen • decreased production of mucin • decreased serum albumin (total plasma protein concentration constant) • increased *alpha* I-GP • increased gamma globulin • decreased red blood cell binding • decreased enzyme induction • decreased hepatic blood flow • decreased hepatic mass • no change in acetylation • decreased glucuronidation • decreased mixed function • decreased production of bile • bile is thicker and richer in cholesterol	H 2 Blockers: cimetidine (Tagamet) ranitidine (Zanctac) famotidine (Pepcid) nizatidine (Axid) Antiacids: Aluminum hydroxide (Amphojel) magnesium hydroxide (M.O.M) calcium carbonate (Tums)	• avoid with use of long-acting benzodiazepines • inhibits hepatic microsomal enzymes • impairs metabolism of warfarin theophylline, and phenytoin (Washington Manual 28, 343) • watch for mental status changes, impotence • no interference with hepatic microsomal enzyme • interfere with absorption of tetracyclines, isoniazid, digoxin, phenothiazines, and irons • recommend taking object drugs 2 hours prior to antacids • avoid using in renal failure • high doses may cause hypercalcemia and hypercalciuria

System	Age-Related Changes	Commonly Prescribed Medications	Pharmacological Responses
Gastrointest-inal (cont.)		Antiemetics: metoclopromide (Reglon) prochlorperazine (Compazine)	• lipid soluble • extensive first pass metabolism in gut wall and liver • Parkinsonian reaction more common in elderly • incidence of Parkinsonism is significantly higher in elderly than younger patients
		Laxatives: anthraquinones (Cascara) Bisacodyl (Dulcolax)	• metabolism and effect not altered in the elderly • excretion depends on renal function • likely cause weakness, sedation, and confusion in elderly • long-term use not recommended • should not be taken within one hour of taking antacids or milk

System	Age-Related Changes	Commonly Prescribed Medications	Pharmacological Responses
Genitourinary	• less acute bladder sensory receptors • urge to void occurs when bladder almost full • bladder contractions intermittent • weakened bladder muscles • normal residual urine of 100 cc • decreased total body water and potassium levels • less rapid and less complete fluid and electrolyte changes • prostate hypertrophy • urethral stenosis or stricture • vaginal secretion diminished • vaginal PH rises • vaginal lining is thinner, drier, and less elastic • altered normal flora • decreased blood flow to penis • loss of functioning nephrons • sclerosis of renal arteries • hyalinization of glomeruli	Antispasmodics: oxybutynin (Ditropan) dicyclomine (Bentyl) Antimicrobials: amino glycosides; amikacin gentamicin netilmicin tobramycin	• monitor anticholinergic side effects; dry mouth, blurred vision, constipation, tachycardia, esophageal reflux, and mental changes • 100% excreted by the kidneys • monitor nephrotoxicity, ototoxicity (often irreversible) • check serum creatinine and creatinine clearance before prescribing

System	Age-Related Changes	Commonly Prescribed Medications	Pharmacological Responses
Genitourinary (cont.)	• decreased renal mass • decreased filtering surface area • decreased plasma renin and plasma aldosterone • decreased renal concentration ability		

System	Age-Related Changes	Commonly Prescribed Medications	Pharmacological Responses
Musculoskel-etal	• decreased lean body mass • increased subcutaneous fat • increased bone absorption (exceed bone formation at age 35) • bone tissue more porous • atrophy of muscle fibers with fibrous and fat tissue • increased lipofuscin (age-related waste material) and fat deposit within muscle tissue • prolongation of contraction time, latency period, and relaxation period of the motor units • loss of elasticity in ligaments, tendons, joints, and synovial membranes (stiffness) • decreased range of motion • decreased size/number of type II muscle fibers • decreased isometric strength • decreased muscle mass • diminished reflexes • resting tremors • muscular fasciculation • impaired extrapyramidal system	NSAIDs salicylates (Aspirin) ibuprofen (Motrin) indomethacin (Indocin) etodolac (Lodine) nabumetone (Relafen) ketoprofen (Orudis) oxaprozin (Daypro) ketorolac (Toradol)	• greatest adverse effect on liver and gastric mucosa • above average risk tinnitus • better analgesic effect • better anti-inflammatory effect • high risk GI and CNS effect • better analgesic effect • little prostaglandin synthesis • little enterohepatic recirculation • non-acid pro-drug • low incidence of GI toxic effects • weak prostaglandin inhibitin effect • long half-life • provides more prolonged analgesic/anti-inflammatory effects • can be used once a day with little or no risk of accumulation • long-acting, long half-life • may accumulate in elderly • high risk GI, renal toxicity • use restricted to 5 days

System	Age-Related Changes	Commonly Prescribed Medications	Pharmacological Responses
Respiratory	• increased AP diameter • decline in chest wall compliance • respiratory muscle weaker • progressive loss of lung elastic recoil • increased residual volume • decreased tidal volume • alveolar membrane thicker • less oxygen defusion • decreased sensitivity of body to oxygen and increased carbon dioxide levels • decreased pulmonary capillary blood volume • longer responsive time to oxygen deficiency • decreased PO2 • less tolerance for exercise and stress • less pulmonary reserve capacity • more susceptible to respiratory disease	Methyxanthines: theophylline	• rapid, complete absorption • 60% protein bound • 85-90% hepatic metabolism • smokers and charcoal containing foods increase absorption by 60% • therapeutic level 10-20 mcq/mL • toxic effect is related to serum concentration • factors affecting theophylline clearance: increase in smoking, phenobarbital, high protein/low CHO diet, charcoal broiled beef, phenytoin, rifampin, carbamazepine • clearance decreased in hepatic cirrhosis, corpulmonale, CHF, fever, propranolol, allupurinol more than 600 mg/day, erythromycin, oral contraceptives
		Sympathomimetics: epinephrine ephedrine isoetharine (Bronkosol) terbutaline (Brethine) metaproteronol (Alupent)	• significant cardiac stimulant effect • less cardiotonic activity • negative response to cardiac stimulation

System	Age-Related Changes	Commonly Prescribed Medications	Pharmacological Responses
Central Nervous System	• loss of neurons in the brain and spinal cord (dramatic after 70) • brain weight decreased • lipofuscin deposits in the neuronal cytoplasm and glial cells • impaired neural conduction • decreased nerve conduction velocity • sensory perception, vision, hearing decreased • decreased synthesis/ metabolism of major neurotransmitters (acetycholine, dopaime, norepinephrine, serotine) • loss of larger nerve fibers in the synaptic chain • reaction time decreased • loss of dendrites (decreased intellectual responsiveness, abstract reasoning, impaired perception) • decreased blood flow and metabolism of brain • decreased visual accommodation (absent after 65 years of age)	Benzodiazapines: long half-life; chlordiazepoxide (Librium) clorazepate (Tranxene) diazepam (Valium) flurazepam (Dalmane) short/intermediate half-life; alprazolam (Xanax) clonazepam (Klonopin) lorazepam (Ativan) oxazepam (Serax) temazepam (Restoril) triazolam (Halcion)	• all are lipid-soluble • most longer-acting benzodiazapines undergo phase I metabolism whereas short/ intermediate acting benzodiazapines undergo phase II metabolism (safer with liver disease) • elderly more prone to develop toxic effects and may experience paradoxic agitation and delirium • monitor development of tolerance and dependency • withdrawal syndrome begins one to 10 days after abrupt cessation of therapy and may last for several weeks (1995, Washington Manual, 28, 8)
		Antidepressants: tricyclics; amitriyptyline (Elavil) desipramine (Norpramin) imipramine (Tofranil) nortriptyline (Pamelor) protriptyline (Vivactil) doxepine (Sinequan)	• undergo oxidation metabolism • caution in patients with glaucoma, prostatic hypertrophy since drug posses potent antihistamine and anticholinergic properties • tricyclic antidepressants are now the leading cause of drug overdose death (1995, Washington Manual, 28, 11) • prescription should be limited to a total of 1 g. Without refills, in the early stages of therapy, when patients appear suicidal

System	Age-Related Changes	Commonly Prescribed Medications	Pharmacological Responses
Central Nervous System (cont.)		Serotonine Re-uptake inhibitors: fluoxetine (Prozac) paroxetine (Paxil) sertraline (Zoloft)	• chemically unrelated to tri and tetracyclics • should not be used in combination with MAOIs (monoamine oxidase inhibitors) or within 14 days of MAOI use as fatal reactions may occur
		MAOIs: phenelzine (Nordil) tranylcypromine (Parnate) isocarboxaizid (Marplan) nialamide (Niamid)	• works by inhibiting enzymes • MAO which are present in the liver and brain • may delay detoxification of stimulants, depressants such as coffee, antihistamine, narcotics, alcohol, and barbiturates • may interact with tyramine containing food such as cheese, beer, canned figs, broad beans, chicken liver, red wines, and yeast • toxic doses can cause strokes, liver damage, hypertensive crisis
		Non-MAO Inhibitors: amitriptyline (Elavil) despramine (Norpramin) imipramine (Tofranil) nortriptyline (Aventyl)	

System	Age-Related Changes	Commonly Prescribed Medications	Pharmacological Responses
Central Nervous System (cont.)		Buspirone (Buspar)	• markedly hepatic metabolized with extensive first pass effect • no tolerance/withdrawal occurs • no hypnotic/sedative effect • requires chronic administration
		Barbiturates: amobarbital (Amytal) butabarbital (Butisol) pentobarbital (Numbutal) secobarbital (Seconal)	• narrow therapeutic index • all barbiturates have an extremely long half-life
		Chloral Hydrate (Noctec):	• contraindicated in marked hepatic or renal impairment • fatal interaction with ethanol • short-term increase in the anticoagulant effect of warfarin (1995, Washington Manual, 28, 8)