Academic Sciences Asian Journal of Pharmaceutical and Clinical Research
Vol 5, Suppl 4, 2012 ISSN - 0974-2441

Review Article

AN OVERVIEW OF GERIATRIC PHARMACOLOGY

POOJA REDDY*[1], DEVESH GOSAVI[2], SUSHIL KUMAR VARMA[2]

[2]Department of Pharmacology, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha, India; [1]Department of Pharmacology, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha, India;Email: drpthakur@gmail.com

Received: 6 September 2012, Revised and Accepted: 16 October 2012

ABSTRACT

Elderly patients frequently experience multiple illnesses and take many drugs concurrently. The combination of altered drug activity, impaired homeostasis, and the use of multiple drugs by elderly patients results in frequent adverse drug reactions. Although they can be difficult to recognize in elderly patients, adverse drug reactions are a frequent cause of morbidity and may necessitate hospitalization. Because the risk of adverse drug reactions increases with the number of drugs taken, it is important to discontinue any treatment that is not efficacious. Because of neurological, visual and auditory disabilities, elderly patients may have difficulty complying with complicated drug regimens. Some chronic diseases in elderly patients cannot be effectively treated with drugs. The survey studies regarding utilization of medicine as well as the education in elderly patients may reduce the morbidity in general. Furthermore, the education and the training of doctors for prescribing drugs in elderly patients in view of altered drug behavior in these patients in view of changed pharmacokinetic and pharmacodynamic behavior of the drugs will be remedial measures to decrease the morbidity of elderly patients to a greater extent.

Keywords:

INTRODUCTION

Society has traditionally classified everyone over 65yrs as elderly. 'Geriatrics' apply to persons over 75yrs[1]. Elderly persons are our most medicated group of patients and are prescribed the highest proportion of medications. Pharmacotherapy is single most important intervention for care of the majority of elderly patients[2]. This group today represents approximately 13% of total population but purchase 33% of all prescription drugs, furthermore, by 2040, it is estimated that they will represent 25% of total population and will buy 50% of all prescription drugs[3]. The number and proportion of elderly people in the population are increasing as a result of decreasing birth rates and improved medical and economic factors that favor a longer life expectancy[4].

The dose of the drug in elderly patient is to be administered cautiously. In the early days, decisions about drug selection and the dosage in the elderly were largely based on trial and error. Sound information on drug disposition and tissue and cellular responses to drugs in the elderly has been obtained only recently.

Adverse drug reactions are an important cause of morbidity and hospital admission in elderly patients[5]. 85 to 95% of ambulatory elderly take at least 1 medication, with an average of 3-4 per day[6,7]. In a large, multicentre trial, adverse reactions were a contributing cause in 10.5% of consecutive geriatric admissions[8]. The enhanced adverse drug reaction may be due to impaired organ function, aging itself, altered drug kinetics and organ response and homeostatic counter-regulation to drug effect. The physiological changes that occur in elderly are shown in Table-1..

Table 1: Physiological Changes in Elderly.

BODY COMPOSITION	↓ in total body water, ↓ in lean body mass, ↑ in fat, ↓ in plasma albumin, ↑ in α1 acid glycoprotein
CNS	↓ in weight and size of brain, cognitive deficit
PULMONARY SYSTEM	↓ in total vital capacity, ↓ in maximum breathing capacity, ↓ in total alveolar surface, ↓ respiratory muscle strength
CVS	↓ baroreceptor activity, ↓ cardiac output, ↑ in total peripheral resistance
GASTROINTESTINAL SYSTEM	↑ in gastric pH, ↓ GIT blood flow, Delayed gastric emptying, ↓ intestinal blood flow
LIVER	↓ in hepatic blood flow
RENAL	↓ in GFR, ↓se renal blood flow, ↓se tubular secretion
GENITOURINARY SYSTEM	Prostatic hypertrophy (Males), Vaginal atrophy and menopause (females), Incontinence
ENDOCRINE	↑se incidence of diabetes and thyroid disorder
IMMUNE SYSTEM	↓ in cell mediated immunity

PHARMACOKINETIC FACTORS

Drug absorption and bioavailability

Bioavailability of a drug depends on gastrointestinal absorption and the first pass metabolism in gastric mucosa and the liver. The process of aging brings about changes in gastrointestinal function such as increase in gastric pH[9], delayed gastric emptying, decreased motility, and decreased intestinal blood flow[10] . The absorption of substances that are actively transported from the intestinal lumen including some sugars, minerals and vitamins may therefore be decreased in elderly patients. Apart from the pathological or surgical alterations in gastrointestinal function such as gastrectomy, pyloric stenosis, pancreatitis, regional enteritis, and malabsorption syndromes[11] and concurrent administration of other drugs like cholestyramine and antacids may cause changes in drug absorption. Cholestyramine binds and decreases the absorption of many drugs including thiazides, anticoagulants, thyroxine, aspirin, PCM,

penicillin while antacids decrease the absorption of drugs such as chlorpromazine, tetracycline, isoniazid[12].

Plasma protein concentrations may also be altered in elderly patients. Plasma albumin concentrations are less causing increase in free concentration of acidic drugs such as naproxane, phenytoin and warfarin. In contrast, the concentration of α1-acid glycoprotein may be increased in the presence of chronic diseases that frequently occur in the elderly population, potentially increasing the binding of drugs such as antidepressants, antipsychotic drugs and β-blockers which are mainly bound to this protein[13].

Drug Distribution

Drug distribution is determined by body composition, plasma protein binding, and organ blood flow. Total body water and lean body mass decreases, whereas, body fat as a percentage of body weight increases with aging. The increased body fat is associated with the increase in volume of distribution of fat-soluble drugs such as the benzodiazepines which leads to a more prolonged drug effect. Thus, it was demonstrated that the elimination half-life of diazepam was prolonged with age despite the fact that systemic clearance was unaltered[14]. Change in organ blood flow with aging may also affect the rate of drug distribution. Some cross-sectional studies indicate that cardiac output decreases and peripheral vascular resistance increases with age[15]. Hepatic and renal blood flow is decreased[16,17].

Hepatic Metabolism

Hepatic blood flow and liver mass change in proportion to body weight and decrease with aging[16]. The rate of metabolism of many drugs by the cytochrome P450 enzyme system is decreased by 20-40% with aging[18]. Examples include theophylline, propranolol, nortriptyline, alfentanil, fentanyl, alprazolam, triazolam, diltiazem, verapamil, and levodopa. Many benzodiazepines are metabolized by microsomal enzyme to active metabolites which are also eliminated by hepatic metabolism. Non-microsomal enzyme pathways may be less affected by age[18]. Example-Ethanol metabolism by alcohol dehydrogenase and isoniazid elimination by acetylation are unchanged in elderly patients. Concurrent drug administration, illness, genetics and environmental factors including smoking may have more important effects on hepatic drug metabolism than age[19].

Renal Excretion

Renal blood flow, glomerular filtration rate and tubular function all decline with aging[17]. In addition to physiological decline in renal function, the elderly patient is particularly liable to renal impairment due to dehydration, congestive heart failure, hypotension and urinary retention, or to intrinsic renal involvement e.g. diabetic nephropathy or pyelonephritis.

As lean body mass decrease with aging, the serum creatinine level is a poor indicator of (and tends to overestimate) the creatinine clearance in older adults. The Cockroft-Gault formula[20] should be used to estimate creatinine clearance in older adults:

$$\text{Creatinine clearance} = \frac{\{140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine in mg/dl}}$$

(For women multiplied by 0.85)

Drugs with significant toxicity that have diminished renal excretion with age include allopurinol, aminoglycosides, amantadine, lithium, digoxin, procainamide, chlorpropamide and cimetidine. These agents have reduced clearance, prolonged half-lives and increased steady-state concentrations if dosages are not adjusted for renal function. The age-related physiological changes as well as changes caused by pathological conditions on pharmacokinetic parameters are shown in Table-II.

Table 2: Physiological changes and pathological conditions affecting pharmacokinetic variables in elderly

Pharmacokinetic variable affected	Age-related physiological changes	Pathological Conditions
ABSORPTION	↑Gastric pH, ↓absorptive surface, ↓splanchnic blood flow, ↓GIT motility	Achlorhydria,diarrhoea, postgastrectomy, malabsorptiion syndrome, pancreatitis
DISTRIBUTION	↓C.O; ↓total body water, ↓lean body mass, ↓serum albumin conc, ↑α1 acid glycoprotein conc, ↑proportion of body fat	Congestive heart failure, dehydration, oedema or ascitis, hepatic failure, malnutrition, renal failure
METABOLISM	↓Hepatic mass, ↓hepatic blood flow	CHF, fever, hepatic insufficiency, malignancy, malnutrition, thyroid disease, viral infection
EXCRETION	↓Renal blood flow, ↓GFR, ↓tubular secretion	Hypovolemia, renal failure

PHARMACODYNAMIC CHANGES

In addition to pharmacokinetic changes, organ response and homeostatic counter-regulation may be altered with aging. The physiological response includes both the direct drug effect and the homeostatic responses to that pharmacological effect. Decreased homeostatic counter-regulation with aging may be a significant cause of adverse drug reactions.

Receptor Sensitivity

β-adrenoceptor function in elderly patients has been more extensively studied than other receptor responses. It appears that the β-adrenoceptor agonist affinity is decreased with aging, perhaps secondary to elevated plasma catecholamine concentrations[21].

Elderly patients are known to be more sensitive to psychotherapeutic drugs. Impairment of psychomotor function by benzodiazepines, for example, occurs at lower concentrations in elderly than in young patients. Elderly patients appear to be more sensitive to the effects of morphine, warfarin, diltiazem, verapamil, enalapril and levodopa[22].

Impaired Homeostasis

Homeostatic regulation requires appropriate sensing of an altered physiological state (whether due to disease or therapeutic intervention), endocrine or neurological transmission of sensory and regulatory signals, and appropriate organ compensatory responses. Impaired homeostasis is a frequent cause of adverse drug reactions as well as increased sensitivity to drug effects. For example, older individuals have an impaired ability to excrete free water load. Addition of hydrochlorothiazide further impairs free water excretion in elderly patients, placing the patient at risk of dilutional hyponatremia[23].

Most of the elderly patients are susceptible to congestive heart failure from the rapid infusion of saline. Cardiac output, renal function and endocrine response to volume overload are all decreased with age.

Volume depletion is also a risk. While the senescent kidney is able to decrease urinary sodium to low concentrations, the adaptive response is delayed and extracellular fluid loss may be significant during this period[24]. Volume depletion is further exacerbated by diminished plasma rennin activity, the basal level of which is decreased by 30 to 50% in elderly patients. The relative decrease with age becomes greater following salt restriction, diuretic therapy, or upright posture[25].

Postural hypotension is frequent in elderly individuals and may be exacerbated by many drugs. The pathogenesis is probably multifactorial and includes decreased baroreceptor response, altered sympathetic activity and responsiveness, impaired vasomotor response in both arterioles and veins, and altered volume regulation. Phenothiazines, tricyclic antidepressants, levodopa, antihypertensive drugs and diuretics are frequent causes of postural hypotension seen in clinical practice.

ADVERSE DRUG REACTIONS IN ELDERLY

The incidence of adverse drug reactions in elderly is 2-3 times more than that seen in young adults. It is seen more between ages of 61-80 yrs. The most consistent risk factor for adverse drug reactions is number of drugs being taken. Risk of adverse drug reactions rises exponentially as the number of drugs increases.

Commonly used drugs which produce unwanted effects in elderly:

1. Postural Hypotension: Isosorbide dinitrate, TCA, Levodopa, antipsychotics, β blockers, diuretics, α blockers.

2. Constipation: Anticholinergics, antidepressants, antipsychotics, opioids, nifedipine

3. Urinary Incontinence: Antipsychotics, β blockers, diuretics, prazosin, lithium, labetalol

4. Depression: Antipsychotics, anxiolytics, β-blockers, methyldopa.

5. Confusional states: Anticholinergics, antihistaminics, sedative-hypnotics, anticonvulsants, antidepressants.

6. Parkinsonism: Antipsychotics, Metoclopramide, Reserpine, methyldopa.

COMMON DRUG INTERACTIONS

Age-related pharmacokinetic and pharmacodynamic changes can potentially increase the risk of adverse events from drug interactions. Cellular, organ, and systems reserves decrease with age. The effects of individual genetics, lifelong living habits, and environment will result in heterogeneity between people as they age[26,27].

Some common drug interactions associated with their risk are listed in Table III

Table 3: Common examples of drug combinations associated with their risk in old age.

Combination	Risk
ACEI + Diuretics	Hypotension
ACEI + Potassium	Hyperkalemia
Antiarrhythmic + Diuretic	Electrolyte imbalance, arrhythmia
BZD + antipsychotics / antidepressants	Confusion, sedation, fall

Some examples of medicines commonly needed in geriatric age group, drugs to be avoided with their reasons and the safer alternatives are discussed in Table-IV

Table 4 : Drugs to be avoided in geriatric age group, the reason to be avoided and their safer alternatives.

Drugs to be avoided	Reason	Safer Alternative
SEDATIVES and HYPNOTICS Chlordiazepoxide Diazepam Barbiturate Flurazepam	Prolongation of half life due to age related decline in renal & hepatic functions. More sensitive on pharmacodynamics basis as well as leading to ataxia, loss of postural reflex and fall causing fractures and injuries	Oxazepam, lorazepam, alprazolam do not form active metabolites and have shorter duration of action and are less sedating.
ANALGESICS Opioids NSAIDS	Elderly are very sensitive to their respiratory depressant effect so use with caution. In chronic conditions such as cancer use is justified. Used carefully as they cause gastric irritation and bleeding and renal damage (cleared primarily by kidneys).	Prefer codein, buprenorphine. Titrate the dose and frequency of administration. Ibuprofen preferred. Corticosteroid may be used with calcium and vitamin D supplement (to avoid osteoporosis)
ANTIPSYCHOTICS Phenothiazine Haloperidol	Avoided because of greater risk of extra pyramidal effects and postural hypertension.	Thioridazine and Olanzepine are safe in this regard.
ANTIDEPRESSANTS Tricyclic antidepressants	Avoided due to postural hypotension and anticholinergic side effects. Combination of antipsychotic + antidepressant should be avoided.	Prefer SSRIs (Fluoxetine). If tricyclic are to be used prefer nortriptiline or desipramine.
ANTIMANIA Lithium	Renal toxicity, Thiazide diuretics further reduces lithium clearance and increases its toxicity.	Dosage must be adjusted appropriately and blood levels monitored.
ALZHEIMER'S DISEASE Tacrine (Cholinesterase inhibitor)	Hepatic toxicity.	Donepezil, rivastigmine, galantamine prefer being safer.
GENERAL ANAESTHETICS Halothane Enflurane Thiopentol	Elderly more sensitive to halothane and more prone to its hepatotoxicity. Enflurane precipitates epilepsy. More sensitive thiopental.	Prefer Isoflurane. For minor surgeries prefer midazolam. Thiopentol and pancurarium should be used in low doses.
ANTIHYPERTENSIVE DRUGS Thiazide diuretics in high doses MethyIdopa Beta-Blockers	Causes hypokalemia, hyperglycemia and hyperuricemia which increase risk of arrhythmias, type 2 DM and gout. Methyldopa produces deep sedation and postural hypotension. Propranolol is not safe in elderly suffering from bronchial asthma, peripheral vascular diseases.	ACE inhibitors, Angiotensin II antagonist, Diuretics in low doses.

CARDIAC GLYCOSIDES	Increase in sensitivity to the toxic antiarrhythmic actions of digoxin. Clearance of digoxin is usually decreased and its half life is prolonged.	Loading doses should be reduced and maintenance dose should also be reduced.
ANTIARRHYTHMIC DRUGS Quinidine Xylocaine	The clearance of quinidine is decreased and its half life is prolonged in elderly. Half life of Xylocaine is also increased in elderly, toxic effect more.	Quinidine and Xylocaine can be used with reduced doses.
ANTIMICROBIAL AGENTS Penicillin Cephalosporins Aminoglycosides	Due to decrease in renal function half life of these drugs prolonged. Aminoglycosides causes nephrotoxiocity. (reversible)	According to some studies, half life of Tobramycin is not prolonged. Use of ceftriaxone and cefoperazone which are excreted through bile. Otherwise dose adjustment.
LAXATIVES and PURGATIVES Castor oil Liquid paraffin	Damage to intestinal mucosa. Small amount may pass into intestinal mucosa to produce foreign body granulomas.	Prefer Ispaghula, bran, Bisacodyl.
ANTIEMETICS Metoclopramide	Avoided due to its extra pyramidal side effects.	Prefer domperidone or ondansetron.
ANTIDIABETIC DRUGS Chlorpropamide Glibenclamide	Half life of these drugs gets increased in elderly. These are known to cause serious side hypoglycemia episodes.	Glipizide and gliclazide may be used.

PRINCIPLES OF PRESCRIBING DRUGS FOR ELDERLY PATIENTS

The following questions are to be answered carefully before prescribing drugs to elderly patients:

- Is drug therapy required?
- If drug treatment is required, which drug is appropriate?
- Is the patient being asked to take more drugs than are tolerable or manageable?
- Which type of preparation should be used?
- Should the standard dosage or dosage schedule be modified?
- Should the drug be specially packaged and labeled?
- Can the patient living at home manage self medication?
- Is there a need for continued medication?
- Is the drug affordable?

Many of the diseases which elderly patients experience either do not require treatment or are not effectively treated with available medications. Many old people admitted to hospital or reviewed during long term hospitalisation improve greatly when the regimen of drugs that they have been taking is stopped[28,29]. These edicts do not mean, however, that drugs should be withheld on account of old age, particularly when appropriate drug treatment can improve the elderly person's quality of life.

The margin between therapeutic effect and toxicity is so small in many cases that a drug which is indicated for a particular condition in younger patients may be unsuitable in elderly patients with the same condition. For example, the age-related toxicity of benzodiazepines with long half-lives has made the use of these drugs undesirable in elderly patients

The smallest number of drugs that the patient actually needs should always be used. The likelihood of toxicity increases as the number of drugs prescribed rises. Medication errors, especially errors of omission, non-comprehension and non-compliance with medication instructions, have long been recognised as occurring in elderly patients[30,31].

The dosage form and the size, shape and colour of tablets and capsules, and their similarity to one another are all important considerations in prescribing drugs to elderly patients[32]. Many older people have difficulty in swallowing; consequently, large tablets and capsules should be avoided. There is a good case for the use of liquid preparations such as syrups for many patients, or of effervescent tablets. On occasion, suppositories may be the most suitable method of administration.

Whenever possible, intermittent schedules such as drugs given on alternate days or 5 days a week should be avoided, since they are rarely followed accurately. Once-daily dosage ensures better compliance than more frequent regimens[33]. Apart from convenience to the patient and better compliance, once daily dosage at night, for example of psychotherapeutic drugs[34,35], may decrease troublesome adverse reactions since the patient would be asleep when these effects would be most annoying.

Where possible, drugs prescribed for elderly patients living at home should be packaged in readily opened containers so that disabled patients in particular are able to use them[36]. Clear labeling in large print is also very important[37]. Blister packaging or unit dose packaging can reduce non-compliance significantly[38,39].

Elderly patients should be taught to understand the drugs they must take, particularly the relative importance of drugs to their well-being. Time should be spent to educate the patient in the use and administration of their regimen. Sometimes it may be necessary to provide clear instructions in writing about the manner in which a drug should be taken or to suggest the use of a diary or calendar to record daily drug administration[40].

When a drug such as digoxin has been prescribed in an acute episode (e.g. atrial fibrillation complicating pneumonia) there may be no reason for its continued use once the acute episode is satisfactorily treated. It is useful to review treatment regularly and discontinue drugs that are no longer needed[28].

Cost-effectiveness is a very important parameter that should be kept in mind while prescribing drugs to the elderly.

POLYPHARMACY IN THE ELDERLY

Polypharmacy means "many drugs" or the use of more medication than is clinically indicated or warranted, or the empiric use of five or more medications[41]. It is surveyed that average use of medicines for persons above 65years of age are 2 to 6 prescription drugs and 1 to 3.4 over-the-counter medicines[42]. Polypharmacy leads to more adverse drug reactions and decreased adherence to drug regimens. Patient outcome is also affected, constituting of poor quality of life, high rate of symptomatology and (unnecessary) drug expense.

The factors that may contribute to polypharmacy though underreported are use of multiple health care providers and others' medications by geriatric patients and limited time for discussion and

diagnostics, limited knowledge of geriatric pharmacology and the power of inertia of the prescribing doctors[43].

Role of Care Provider in Polypharmacy

At least yearly, and more often if indicated, ask elderly patients to bring in all medications they have at home including their prescription, over-the-counter medicines, vitamins supplements, herbal preparations, etc. The use of vitamins and herbal products in elderly people is very common and generally not reported to the physician. Some serious drug interactions are possible, e.g. with Warfarin, gingko biloba, vitamin E.

What should a care provider do with the 'Brown Bag full of bottles'? He should document and determine indication, prioritize vital vs. optional and cure vs. relieve symptom drugs, discuss with the patient and caregiver, plan for medication reduction. Discontinuing unnecessary medications is one of the most important aspects of decreasing polypharmacy. Drugs without indications should be stopped[44].

REFERENCES

1. Bertram G. Katzung. Special aspects of geriatric pharmacology. *In, Basic and Clinical Pharmacology*, 9th edition. 2004, 1007-1014
2. Fundamentals of geriatric medicine: a case-based approach. By Rainier P. Soriano, Helen M, Fernandez. Chapter 3: *Geriatric Pharmacology and Drug Prescribing for Older Adults*. 4th Edition (2007), Pg-39.
3. Semla TP, Rochon PA. *Pharmacotherapy, Geriatric Review Syllabus*. 5th edition. USA: Blackwell, 2002: 37
4. Therese Hesketh, Li Lu, and Zhu Wei Xing. The effect of China's one-child family policy after 25 years. *N Eng J Med* 2005; 353: 1171-6.
5. Beard K. Adverse reactions as a cause of hospital admission for the aged. *Drugs and aging* 1992; 2: 356
6. Hale WE, May FE, Marks RG, et al. Drug use in an ambulatory elderly population: a 5-year update. *Drug Intelligence and Clinical Pharmacy* 1987; 21:530
7. Helling DK, Lemke JH, Semla TP, et al. Medication use characteristics in the elderly: the Iowa 65+ rural health study. *J Am Geriatr Soc* 1987; 35: 4
8. Williamson J, Chopin JM. Adverse reactions to prescribed drugs in the elderly: a multicentre investigation. Age and Ageing 1980; 9: 73
9. Kekki M, Samloff IM, Ihamaki T, et al. Age- and sex- related behaviour of gastric acid secretion at the population level. *Scandinavian Journal of Gastroenterology* 1982; 17: 737
10. Bender AD. Pharmacologic aspects of aging: a survey of the effect of age on drug activity in adults. *J Am Geritr Soc* 1964; 12: 114
11. Parsons RL. Drug absorption in gastrointestinal disease with particular reference to malabsorption syndromes. *Clinical Pharmacokinetics* 1977; 2: 45
12. Welling PG. Interactions affecting drug absorption. *Clinical Pharmacokinetics* 1984; 9: 404
13. Sjoqvist F, Alvan G. Aging and drug disposition-metabolism. *Journal of Chronic Diseases* 1983; 36: 31
14. Klotz U, Avant GR, Hoyumpa A, et al. The effect of age and liver disease on the disposition and elimination of diazepam in adult man. *J Clin Inv* 1975; 55: 347
15. Brandfonbrener M, Landowne M, Shock NW. Changes in cardiac output with age. *Circulation*1955; 12: 557
16. Woodhouse KW, Wynne HA. Age-related changes in liver size and hepatic blood flow: the influence on drug metabolism in the elderly. *Clinical Pharmacokinetics*1988; 15: 287
17. Lindeman RD. Changes in renal function with aging: implications for treatment. *Drugs and Aging* 1992; 2: 423
18. Durnas C, Loi C-M, Cusack BJ. Hepatic drug metabolism and aging. *Clinical Pharmacokinetics* 1990; 19: 359
19. Vestal RE, McGuire EA, Tobin JD, et al. Aging and ethanol metabolism. *Clinical Pharmacology & Therapeutics* 1977; 21: 343
20. Cockcroft DW, Gault MH, Prediction of creatinine clearance from serum creatinine, *Nephron* 1976; 16: 31-41.
21. Feldman RD, Limbird LE, Nadeau J, Robertson D, Wood AJ. Alterations in leukocyte beta-receptor affinity with aging. A potential explanation for altered beta adrenergic sensitivity in the elderly. *N Engl J Med* 1984; 310: 815-9
22. Cusack B, Vestal RE. Clinical pharmacology. In: Abrams WB, Beers MH, Berkow R, editors. *The Merck Manual of Geriatrics.* 2nd ed. Whitehouse Station, New Jersey: Merck Research Laboratories 1995: 255
23. Clark BA, Shannon RP, Rose RM. Increased susceptibility to thiazide-induced hyponatremia in the elderly. *J Am Soc Nephrol* 1994; 5: 1106-11
24. Epstein M, Hollenberg NK. Age as a determinant of renal sodium conservation in normal man. *J Lab Clin Med* 1976; 87: 411-7
25. Crane MG, Harris JJ. Effect of aging on renin activity and aldosterone excretion. *J Lab Clin Med* 1976; 87: 947-59
26. Cusack BJ. Pharmacokinetics in older persons. *Am J Geriatr Pharmacother* 2004; 2: 274–302
27. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004; 57: 6–14.
28. Burr ML, King S, Davies HE, Pathy MS. The effects of discontinuing long term diuretic therapy in the elderly. *Age and Ageing* 1977; 6: 38-45
29. Learoyd BM. Psychotropic drugs and the elderly patients. *Aust.N.Z.J.Med* 1972; 1: 1311
30. Schwartz D, Wang M, Zeitz L, Goss ME. Medication errors made by elderly, chronically ill patients. *Am J Public Health* 1962; 52: 2018-29
31. Parkin DM, Henney CR, Quirk J, Crooks J. Deviation from prescribed drug treatment after discharge from hospital. *Br Med J* 1976; 2:686-8
32. Mazullo J. The nonpharmacologic basis of therapeutics. *Clin Pharmaco Ther* 1972; 13: 157-8
33. Eisen SA, Miller DK, Woodward RS, et al. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med* 1990; 150: 1881-4
34. Ayd FJ. Once-a-day neuroleptic and tricyclic antidepressant therapy. International *Drug and Therapeutics Newsletter* 1972; 7: 33-40
35. Ayd FJ. Single daily dose of antidepressants. *JAMA* 1974; 230: 263-4
36. Law R, Chalmers C. Medicines and elderly people: a general practice survey. *Br Med J* 1976; 1: 565-8
37. Morrow D, Leirer V, Sheikh J. Adherence and medication instructions: Review and recommendations. *J Am Geriatr Soc* 1988; 36: 1147-60
38. Murray MD, Birt JA, Manatunga AK. Medication compliance in elderly outpatients using twice-daily dosing and unit-of-use packaging. *Ann Pharmacother* 1993; 27: 616-21
39. Wong BS, Norman DC. Evaluation of a novel medication aid, the calendar blister-pak, and its effect on drug compliance in a geriatric outpatient clinic. *J Am Geriatric Soc* 1987; 35: 21-6
40. Wandless I, Davie JW. Can drug compliance in the elderly be improved? *Br Med J* 1977; 1: 359-61
41. Michocki RJ. Polypharmacy and principles of drug therapy. In: Daly MP, Weiss BD, delman AM, eds. 20 common problems in geriatrics. New York: McGraw-Hill, 2001:69-81
42. Stoller EP. Prescribed and Over-the-Counter Medicine Use by the ambulatory elderly. *Med Care* 1988; 26: 1149-1157
43. CM Williams. Using Medications Appropriately in Older Adults. *Am Fam Physician*. November 15, 2002; 66: 1917-1923
44. Carlson JE. Perils of polypharmacy: 10 steps to prudent prescribing. *Geriatrics* 1996; 51: 26-30, 35.