

Rational Drug Therapy in Elderly

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Introduction

Older the person, greater are the ordeals – Goethe

Treatment in elderly patients appears complex and frightening to the uninitiated but it has its rewards. Principles of treatment in elderly are -

1. Usually there are multiple abnormalities amenable to treatment and small improvement in each may yield dramatic overall benefit.
2. The treatment of contributing factors is at times more rewarding than the treatment of disease itself e.g. in a patient of mild Alzheimer's disease with depression and deafness; treatment of deafness and depression may restore the functional independence of patient more rapidly and at lesser cost than the treatment of Alzheimer's disease. Hence, in an elderly you have to treat the patient as a whole (holistic approach) and not the disease only.
3. Under treatment in elderly is quite common due to fear of side effects e.g. chronic atrial fibrillation in elderly is usually not treated with anticoagulants due to fear of intracranial bleed, though studies have clearly proven that anticoagulant treatment has favorable risk benefit ratio and should be given.
4. Set priorities in evaluation and treatment that are most likely to benefit. These priorities should be based upon patient's goals for care, life expectancy, prevalence of specific disease, results of screening or diagnostic tests and effectiveness of therapeutic interventions. Thus, tight glycemic control may be abandoned, if it means placement in nursing home for an elderly with life expectancy of less than 5 years.
5. Geriatric physician often grapple with ethical

dilemmas. Older patients are particularly vulnerable and family members may have to be involved in decision making like surgery or nursing home placement. The physician must be knowledgeable about the complexities of medical care in elderly.

6. Geriatrics is inherently interdisciplinary. A well functioning, interdisciplinary team is critical for comprehensive care of elderly. At the same time geriatric care needs involvement of family or caregiver to ensure compliance. Attention should also be given to the needs and health of caregiver to ensure long term care of elderly patient.

Rational drug use assumes significance in elderly as they use more prescribed and over the counter (OTC) drugs than the younger population. Various factors are responsible for the 3-7 times greater incidence of adverse drugs reactions (ADRs) in the elderly as compared to the age group 20-29 years.¹ Up to 30% of drug intake may result in ADRs contributing to 10% of hospital admissions in elderly.² The decline in physiological reserve in the geriatric population results in poor compensation and recovery from ADRs.³ Elderly population should receive drugs only for well defined indications at the lowest effective doses.

The peculiar problems of drug therapy in the elderly are enumerated in Table 1.

Table 1: Problems of drug therapy in the elderly

Problems faced by patients

1. Increased incidence of ADRs
2. Poor compliance

Problems faced by doctors

1. Non-homogenous group of patients with variable physiological decline
2. Multiple co-morbidities
3. Communication problems
4. No drug trials in elderly
5. Self medication by patient

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I. Increased incidence of ADRs in elderly

These may be due to the following factors:

- A. Changes in pharmacokinetics
- B. Changes in pharmacodynamics
- C. Drug interactions
- D. Inappropriate prescribing in elderly
- E. Co-morbidities

A. Changes in pharmacokinetics

Pharmacokinetics is “what the patient does to the drug”. In the elderly, changes in absorption, distribution or metabolism of drugs may render them more susceptible to drug-related risks (Table 2).⁴⁻⁷

a. Absorption of drugs

Changes in the physiology of the gastrointestinal tract with advancing age are not usually of clinical significance but may affect the absorption of orally administered drugs.^{4, 5}

b. Distribution of drugs

In elderly, there is a decrease in body water and an increase in body fat, which affects volume of distribution (Vd) of drugs. Thus, water soluble drugs like digoxin have increased concentration, whereas lipid soluble drugs like diazepam, chlorthalidone, thiopentone sodium have a greater volume of distribution and longer half life ($t_{1/2}$).

c. Drug metabolism

Interindividual variability in drug metabolism is common in the elderly.

Hepatic clearance: Over the age of 30 years, there is approximately 1 percent per year decline in liver blood flow and liver mass. A decrease in first pass effect results in higher serum levels of propranolol, metoprolol, verapamil, nitrates, acetaminophen and tricyclic antidepressants (TCA). The decreased hepatic microsomal enzyme activity prolongs duration of action of benzodiazepines, warfarin and phenytoin.⁸

Renal clearance: Aging is associated with a significant reduction in renal mass and number as well as size of nephrons. Glomerular filtration rate, tubular secretion and renal blood flow decrease by 0.5, 0.5 and 1 percent per year respectively over the age of 20 years.^{9, 10} Tubular secretion and glomerular filtration may not decline in parallel.¹¹ A variable decline in renal clearance occurs with aging. It may affect drugs eliminated primarily by the kidneys e.g. aminoglycosides, atenolol, lithium and digoxin.

Thus, increased volume of distribution (Vd) and or decreased renal or hepatic clearance (Cl) results in increased half life ($t_{1/2}$) for a number of drugs like diazepam, propranolol and aminoglycosides. (Table 3)

B. Changes in Pharmacodynamics

Pharmacodynamics is defined as “what the drug does to the patient”. Theoretically, altered pharmacodynamics could be due to altered sensitivity owing to changes in receptor number, affinity and post-receptor response or age-related impairment of physiological and homeostatic mechanisms.¹² Some common changes in pharmacodynamics with aging are shown in Table 4.

Table 2: Age – related changes in drug pharmacokinetics^{4, 5, 6, 7}

Pharmacokinetic phase	Pharmacokinetic parameters
Gastrointestinal absorption	Unchanged passive diffusion and no change in bioavailability for most drugs. ↓ active transport and ↓ bioavailability for some drugs ↓ first – pass effect and ↑ bioavailability for some drugs
Distribution	↓ Volume of distribution, ↑ plasma concentrations of water soluble drugs. ↑ volume of distribution and ↑ terminal disposition half – life ($t_{1/2}$) for fat-soluble drugs ↑ or ↓ free fraction of highly plasma protein bound drugs.
Hepatic metabolism	↓ clearance and ↑ $t_{1/2}$ for some oxidatively metabolized drugs ↓ clearance and ↑ $t_{1/2}$ of drugs with high hepatic extraction ratio
Renal excretion	↓ clearance and ↑ $t_{1/2}$ of renally eliminated drugs

Table 3: Some important alterations in pharmacokinetics of drugs with aging

Drug	Vd	t ½	Cl	Recommendations
Aminoglycoside	U	I	D	Reduce dose or increase dosing interval
Atenolol	U	I	D	Assess efficacy clinically
Diazepam	I	I	D	Assess efficacy clinically
Digoxin	D	I	D	Reduce dose
Frusemide	I	I	D	No change in dose required as there is decrease in receptor sensitivity
Lidocaine	I	I	D	Reduce dose
Lithium	?	I	D	Reduce dose
Phenytoin	I	?	I	Monitor drug levels, adjust dose with caution
Quinidine	U	I	D	Reduce dose
Ranitidine	?	I	D	Reduce dose
Theophylline	U	I	D	Measure drug levels

U- Unchanged; D- Decreased; I- Increased, Vd- Volume of distribution; t ½ - Half – life; Cl- Clearance

Table 4: Some common changes in pharmacodynamics with aging

Drugs	Changes	Recommendations
Antihypertensive agents	Increased risk of orthostatic hypotension	Use cautiously
Benzodiazepines	Increased sensitivity	Use lower maintenance dose
β-adrenergic blockers	Decreased β-adrenergic responsiveness	Monitor efficacy / action clinically
Coumarin anticoagulants	Increased sensitivity	Use lower maintenance dose
Diuretics	Increased susceptibility for complication	Monitor electrolytes & orthostatic hypotension

a. Altered Sensitivity

Older patients are generally more sensitive to the doses or plasma levels of a number of medications considered appropriate for younger patients e.g. sedatives, psychotropic drugs, narcotic analgesics (opiates), digoxin, theophylline and phenytoin. For some drugs like β-adrenergic blockers and β-agonists there are decreased receptors.

b. Age related impairment of physiological and homeostatic mechanisms

Physiological and homeostatic impairments in elderly people that may affect drug response include autonomic nervous system dysfunction (orthostasis, bowel and bladder dysfunction), impaired thermoregulation, reduced cognitive function reserve, impaired postural stability, glucose intolerance, and immunosenescence.¹³⁻¹⁷

Changes in homeostasis: Adverse pharmacodynamic effects are common and more significant in the elderly due to physiological decline

and co-morbidities. Mildly nephrotoxic drugs like NSAIDs may have disastrous consequences in elderly individuals with impaired renal function at baseline.

Orthostatic hypotension: Due to blunting of baroreceptor reflex, postural hypotension in elderly is aggravated by antihypertensives as well as by neuroleptics, TCA, benzodiazepines and anti-parkinsonian drugs.

CNS: Postural control is poor in the elderly. Sedative drugs accentuate it, leading to increased falls and injuries. Neurotransmitters in the CNS decrease with age. Drug related confusion increases in elderly with theophyllines, β-blockers, anticholinergics and hypnotics.

Temperature control: Thermoregulation is blunted with aging. Alcohol, barbiturate, neuroleptics and TCA potentiate hypothermia while anticholinergics aggravate hyperthermia.

Though any drug can cause ADRs, the commonly used ones are most often implicated (Table 5). The

Table 5: ADRs with some commonly used drugs

Drug category	Example	Type of ADR
Sedatives	Benzodiazepines	Delirium
	Diphenhydramine (OTC & prescribed)	Worsening of dementia
Anticholinergics	Sedating analgesics	Urinary incontinence
	Antipsychotics (Neuroleptic)	Postural instability, aspiration
Anticholinergics	Antihistamines (OTC)	Delirium
	Antidepressants (TCA)	Worsening of dementia
	Bladder relaxants	Angle closure glaucoma
	Antipsychotics	Urinary retention
Dopamine receptor blocking agents	Antipsychotics	Extrapyramidal motor system reactions
Aminoglycosides	Metoclopramide	
	Chlorpromazine	
	Gentamycin	Renal failure
NSAIDs	Amikacin	
	Indomethacin	Gastric irritation
	Aspirin	Chronic blood loss
		Renal failure

most common medications are cardiovascular, gastrointestinal, central nervous system, analgesics and vitamins. Other drugs with ADRs are antihypertensives, bronchodilators, digitalis, oral hypoglycemic, anti-parkinsonian drugs, anticoagulants, and anti-arrhythmics. Barbiturate group of drugs should be used with caution because of erratic and occasionally paradoxical effects. Long acting benzodiazepines (diazepam, chlordiazepoxide) cause CNS depression and should be avoided in elderly. When using digoxin, the initial dose should be based on lean body weight and the maintenance dose on creatinine clearance. If possible, try to avoid use of H₁ blockers in elderly, as they are more likely to cause mental confusion or disorientation. Higher doses of iron preparations are needed due to poor absorption in elderly. Levodopa may cause hypotension, syncope or disorientation, hence start low and go slow. Phenytoin toxicity is due to increased free drug levels.

C. Drug interactions

Drug interactions are not only with drugs (Table 6) but also with nutrients (Table 7) or diseases (Table 8) and all these may have significant adverse effects in elderly. Drug-drug interactions are common in elderly due to polypharmacy, which is necessary in patients with multiple comorbidities. Often elderly use a number of OTC drugs or herbal preparations along

with prescribed drugs.

D. Inappropriate prescribing in elderly:

It is defined as overuse of drugs, irrational choice of drugs and/or under use of appropriate drugs. In elderly, overuse of drugs is quite common and they often keep using drugs beyond prescription. Moreover, they are prone to self medication. Use of fixed dose combinations often adds to the problem. Wherever possible, non-pharmacological treatment should be used first.

Common non pharmacological treatment options are:

- Physiotherapy for osteoarthritis / peri-arthritis
- Dietary and lifestyle intervention for diabetes mellitus (Type 2) and hypertension
- Support services for isolation
- Speech therapy for dysphasia
- Relaxation therapy for insomnia

E. Co-morbidities

Co-morbidities add to adverse drug reactions. A drug with even mild anticholinergic effect may cause acute urinary retention in elderly with benign prostatic hypertrophy (BPH) or may precipitate dementia with mild Alzheimer's disease.

Table 6: Drug – drug interaction

Drug	Interacting drug	Result
Digoxin	Quinidine, Verapamil Propranolol Diuretics Spironolactone, Rifampicin Antacids	↑ Digoxin levels ↑ AV block, ↓ inotropic effect of digitalis ↑ digoxin ADRs, due to hypokalemia ↓ digitalis level by ↑ metabolic clearance ↓ digitalis level by ↓ bioavailability
β-blockers	Quinidine, Verapamil	↑ AV block
ACE inhibitors	Potassium-sparing diuretics	hyperkalemia
Anticoagulants	Allopurinol, Metronidazole Aspirin, Cotrimoxazole	↑ t _{1/2} ↑ free drug (protein displacement)
NSAIDs	Antihypertensives	↓ effect
Theophylline	β-blockers, Corticosteroids	↑ levels
Rifamycin	Corticosteroids	↓ effect of corticosteroids
Phenytoin	INH, Chloramphenicol	↑ levels of phenytoin
TCA	Anticholinergic drugs	cholinergic crisis
Lithium	Indomethacin	Lithium toxicity

II. Compliance

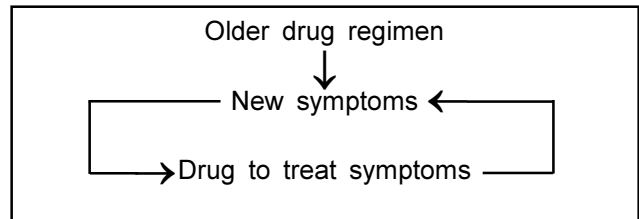
The elderly are generally more compliant than the younger population. However, many factors can lead to poor compliance in this group, resulting in treatment failure. Over 10% of hospital admissions are attributed to medical non-compliance. Common causes of poor compliance are:

- Living alone
- Polypharmacy
- Multiple daily dosages
- Frequently changed drug regimen
- Dependence – more than one provider of drug
- Poor cognition / vision / dexterity
- Improper provision of drug

The strategies to improve compliance are outlined in Table 9.

Rational prescribing in elderly

1. *Proper selection of drug:* The physician should address the question whether drug treatment is at all required. Non-pharmacological means should be considered first. Prescribing for each symptom or sign should be discouraged and stress should be laid upon diagnosing the cause by proper analysis and investigation. It should always be kept in mind that symptoms requiring treatment may be due to ADRs of previous drug regimen rather than new medical condition and adding new drug results in a prescribing cascade.



Checklist for proper selection of drug in elderly

- Is treatment necessary?
- Is this the safest drug available?
- Is it effective?
- Is it acceptable to patient?
- Do the benefits outweigh the risks?
- Is this the most appropriate dose, route of administration and dosage form?
- For how long is the medication required?

2. Keep in mind pharmacokinetics, pharmacodynamics, comorbidities, drug interactions, likely ADRs of the drug to be prescribed and that toxicity can occur even with normal serum levels.

3. Take a good drug history, including prescribed, OTC and herbal drugs; problems with previous regimens, any likely difficulty in handling of drugs and swallowing; examine the drug list.

4. Start low dosages, increase slowly till effect or toxicity is reached; give enough time for drug to act.

Table 7: Drug and nutrient interaction

Effect on Nutrient	Drug taken
↑ Energy intake	TCA, neuroleptics
↓ Energy intake	Metformin, digoxin, cytotoxic drugs
↓ Vitamin levels- B ₆	INH, L-Dopa
- Folic acid	Methotrexate, phenytoin
Electrolytes - ↑ Potassium	Potassium-sparing diuretics, ACE inhibitors
- ↓ Sodium	Diuretics

Table 8: Drug disease interaction

Drug	Adverse effect on disease
Sodium salt of drugs	Congestive Heart Failure(CHF)
Non steroidal anti inflammatory drugs	Chronic Renal Failure, CHF, Hypertension, Peptic ulcer
β-blockers	CHF, Asthma
TCA	Seizures, Bundle Branch block, Postural hypotension
Thiazide	Hypercalcemia, Gout, Diabetes mellitus
Lithium, Amiodarone	Thyroid disease

Table 9: Strategies to improve compliance in elderly

1. Making drug regimens and instructions as simple as possible:
 - Link it with daily routine like meals
 - Use same dose schedule whenever possible. Avoid frequent changes
 - Keep burden of pills low
 - Assure pills can be taken easily, i.e. easy to swallow (small size), patient has no swallowing problem
 - Easy handling of drugs – easy to open drug bottles / packs, clear and large labeling and instructions
 - Educate patient and care givers – counseling, clear instruction both verbal and written, in hospital training on drug regimen and their problems
2. Keep update medicine record/use aids such as medicine calendars
3. Review periodically for knowledge of drug regimens/compliance and inspect drug list.

5. Not only overuse but in elderly under-prescription is also very common especially with drugs like anticoagulants, where risk of bleeding is exaggerated or bronchodilators where larger doses are needed.

6. Always review whether a drug may be safely withdrawn. A drug that does not have clear beneficial effect on a defined end point, should be discontinued. If the patient is not taking or is taking it erratically, the drug may be withdrawn.

Summary

Rational drug use, though important at all ages, becomes more relevant in the elderly as they use more medications than the younger population in the form of prescribed and over the counter (OTC) drugs. Due

to various factors, they have 3-7 times greater incidence of adverse drugs reactions (ADRs) as compared to the latter. As the elderly have a narrow therapeutic window, the physician should use drugs only if non-pharmacological means fail. New signs and symptoms should always be considered as possible consequences of current medication. Use medications in the smallest number, the lowest dosage for the shortest period and with the simplest regimen. The elderly present the clinician with a complex therapeutic challenge but the rewards of rational prescribing are also considerable.

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