Drug Use in the Elderly

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Therapeutic Considerations in the Elderly

- **Elderly patients are those 65 years of age and older.**
- **The health characteristics of those 65-74 years of age are different from those who are 85 years of age and older.**
- **Institutionalized individuals are also different from those living in the community.**
- **Age-related changes in physiology can affect the pharmacokinetics and pharmacodynamics of drugs.**

Therapeutic Considerations in the Elderly

- **Drug-related problems in older adults are common and cause significant morbidity.**
- **Common medical conditions in the elderly include: hypertension, diabetes mellitus, osteoporosis, bronchial asthma, COPD, cancer, arthritis, heart diseases, Alzheimer's disease and cognitive dysfunction, and stroke.**
- **The most common sensory impairments are: difficulties in hearing and vision.**
- **The elderly are also prone to falls.**

Human Aging & Changes in Drug Pharmacokinetics and Pharmacodynamics

Clinical manifestations of normal aging include:

1. **Changes in biochemical makeup of tissues.**
2. **Reduced functional capacity of body systems.**
3. **Reduced ability to adapt to physiological stress.**
4. **Increased vulnerability to disease.**
5. **Frailty (weakness, fatigue, weight loss and functional decline). (ضعف و هشاشة)**

- **Individuals experience aging at different rates.**

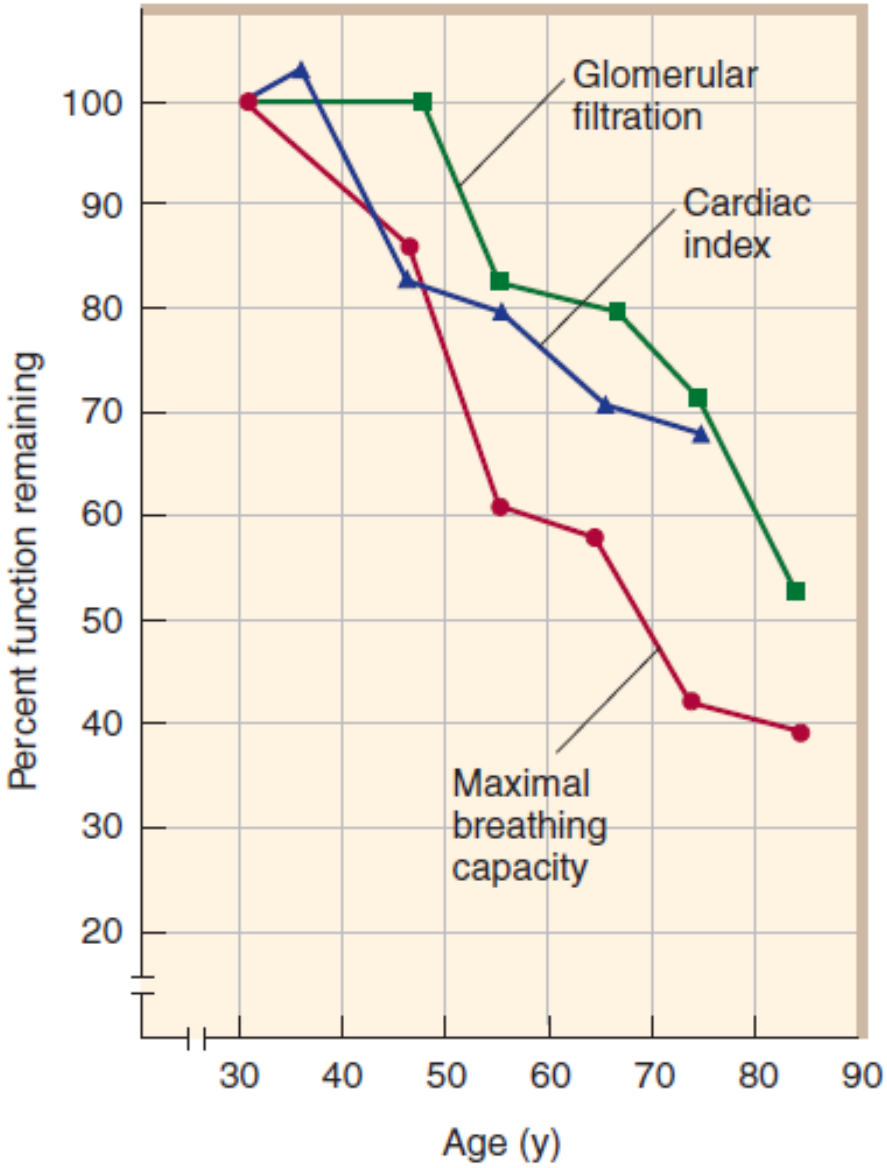

FIGURE 60–1 Effect of age on some physiologic functions.

(Modified and reproduced, with permission, from Kohn RR: *Principles of Mammalian Aging*. Prentice-Hall, 1978.)

TABLE 60–1 Some changes related to aging that affect pharmacokinetics of drugs.

Variable	Young Adults (20–30 years)	Older Adults (60–80 years)
Body water (% of body weight)	61	53
Lean body mass (% of body weight)	19	12
Body fat (% of body weight)	26–33 (women)	38–45
	18–20 (men)	36–38
Serum albumin (g/dL)	4.7	3.8
Kidney weight (% of young adult)	(100)	80
Hepatic blood flow (% of young adult)	(100)	55–60

Common Physiological Changes Associated with Aging

These changes include:

a) **Reduced functional reserve capacity.**

b) **Reduced ability to maintain homeostasis, making them susceptible to de-compensation in stressful situations.**

Examples of such impaired homeostatic mechanisms:

1) **Postural or gait stability**
2) **Orthostatic blood pressure responses**
3) **Thermoregulation**
4) **Cognitive reserve**
5) **Bowel or bladder function.**

Age-Related Altered Drug Pharmacokinetics

Absorption:

1. **Absorption of drugs may be affected by age-related changes in GIT physiology, drug-food interactions, concurrent medication, and co-morbidities affecting GI function.**

- **The bioavailability of drugs absorbed by passive diffusion may not be affected significantly.**
- **Drugs absorbed by active transport (vitamin B_{12}, calcium, iron, magnesium) may have impaired absorption.**

Age-Related Altered Drug Pharmacokinetics

2. First-pass effect is decreased, bioavailability and plasma concentration are increased for drugs such as propranolol and labetolol.
3. There is reduced bioavailability of some pro-drugs such as enalapril and codeine.
4. In atrophic gastritis, or in patients taking gastric acid-lowering agents, extent of absorption of some drugs may be reduced (ketoconazole, iron, digoxin, and atazanavir). These drugs require an acidic environment for absorption.

Age-Related Altered Drug Pharmacokinetics

Distribution:

Factors that influence drug distribution in the elderly:

1. **Altered plasma protein concentrations**
2. **Individual body composition (body fat and intracellular fluid content)**
3. **Decreased muscle and tissue mass**
4. **Reduced blood flow to tissues and organs.**
5. **Active uptake into tissues may also be influenced by ageing.**

Age-Related Altered Drug Pharmacokinetics

- **The volume of distribution of water-soluble drugs (ethanol, gentamicin, digoxin, and cimetidine) is reduced.**
- **Lipophilic drugs (benzodiazepines, metronidazole, and rifampin) exhibit an increased volume of distribution.**
- **Changes in the volume of distribution affect loading doses of drugs.**

Age-Related Altered Drug Pharmacokinetics

- **The brain of elderly patients may be exposed to higher concentrations of drugs and toxins because of age-related changes in the blood-brain-barrier.**

Age-Related Altered Drug Pharmacokinetics

Metabolism:

- **Hepatic metabolism of drugs depends on liver perfusion, activity and capacity of drug metabolizing enzymes, and protein binding.**
- **All of these factors are affected by the aging process.**

➢ **For drugs that have high intrinsic clearance (high hepatic extraction ratio), hepatic clearance depends on hepatic blood flow mainly (flow-limited metabolism).**

Age-Related Altered Drug Pharmacokinetics

- **Age-related decreases in hepatic blood flow (20-50%) can decrease significantly the metabolism of high extraction ratio drugs (propranolol, amitriptyline, diltiazem, lidocaine, metoptolol, morphine and verapamil).**

➢ **For drugs that have low intrinsic clearance (low hepatic extraction ratio), clearance depends on hepatic enzyme activity (capacity-limited metabolism).**

Age-Related Altered Drug Pharmacokinetics

- **Generally, liver size and its enzyme content are reduced in the elderly.**
- **Hepatic metabolism of warfarin, piroxicam and lorazepam is reduced with aging.**
- **Metabolism of phenytoin, ibuprofen, and naproxen is increased with aging.**
- **Metabolism of diazepam, temazepam, and valproic acid is NOT affected with aging.**

Age-Related Altered Drug Pharmacokinetics

- **Serum albumin concentration declines with age.**

✓ **For capacity-limited metabolism, the fraction of the drug unbound will increase for drugs with extensive protein binding, leading to increased total hepatic clearance (naproxen).**

- **Generally, phase II drug metabolism, in contrast to phase I, is preserved in the elderly.**
- **Frail older adults may experience reduced phase II drug metabolism as well.**

Age-Related Altered Drug Pharmacokinetics

Elimination:

- **Age-related reductions in GFR are well documented.**
- **Serum creatinine is a poor indicator of renal function in the elderly because creatinine is produced by muscles and there is reduced muscle mass in the elderly.**

Age-Related Altered Drug Pharmacokinetics

- **Cockcroft and Gault equation may be used to calculate creatinine clearance:**

$$\text{Creatinine clearance} = \frac{(140 - \text{Age})\,(\text{Actual body weight})}{72\,(\text{Serum creatinine concentration})}$$

Multiply the result by 0.85 for females.

➢**You should measure CL_{cr} accurately when you plan dose adjustment in patients with reduced renal function.**

Age-Related Altered Drug Pharmacokinetics

- **Dosing guidelines of drugs that are eliminated by the kidney are based on creatinine clearance.**

✓ **Some drugs should be avoided when CLcr < 30 mL/min: colchicine, co-trimoxazole, glyburide, nitrofurantoin, probenecid, spironolactone, triamterene.**

✓ **Some drugs need dose reduction in reduced renal function: acyclovir, amantadine, ciprofloxacin, gabapentin, ranitidine.**

Age-Related Altered Drug Pharmacodynamics

- **Changes in PDs are less understood than changes pharmacokinetics.**

Proposed changes leading to altered pharmacodynamics of drugs may include:

1. **Changes in drug concentration at the receptor.**
2. **Changes in receptor numbers.**
3. **Changes in receptor affinity.**
4. **Post-receptor changes.**
5. **Age-related changes in homeostatic mechanisms.**

Age-Related Altered Drug Pharmacodynamics

Older adults are more sensitive to the CNS effects of drugs:

1. **Changes in size and weight of brain.**
2. **Changes in the neurotransmitter systems.**
3. **Drugs penetrate CNS easier than in young adults.**

- **For example, in the elderly there is decreased levels of dopamine transporters, decreased number of dopaminergic neurons, and decreased density of dopamine receptors; leading to increased sensitivity to the adverse effects of antipsychotic drugs.**

Age-Related Altered Drug Pharmacodynamics

- There is increased sensitivity to benzodiazepines, opioids, general anesthetics antipsychotics, lithium and anticholinergic drugs.
- The elderly are more likely to develop orthostatic hypotension as an adverse effect of some drugs.

Age-Related Altered Drug Pharmacodynamics

There is also:

- **Increased hypotensive and bradycardic effect to calcium channel blockers.**
- **Reduced blood pressure response to β-blockers.**
- **Reduced effectiveness of diuretics.**
- **Increased risk of bleeding with warfarin.**

Drug-Related Problems in the Elderly

Include 3 important, potentially preventable, negative outcomes:

1. **Withdrawal effects.**
2. **Therapeutic failure.**
3. **Adverse drug reactions.**

Drug-Related Problems in the Elderly

Risk Factors:

1. **Polypharmacy including prescription and non-prescription drugs, herbal medicines, supplements and unnecessary drugs.**

- **Polypharmacy has been strongly associated with ADRs, risk of geriatric syndromes (falls, cognitive impairment), non-adherance, diminished functional status, and increased health care costs.**

Drug-Related Problems in the Elderly

2. **Inappropriate Prescribing, which includes:**

a. **Wrong dose and duration.**

b. **Duplication.**

c. **Drug interaction problem.**

d. **Prescription of drugs that should be avoided in the elderly. *********

3. **Underuse:**

- **Omission of drug therapy that is indicated in prevention or treatment of disease.**

Drug-Related Problems in the Elderly

4. Medication non-adherence:

Causes:

a. **Adverse effects.**
b. **Complex regimens.**
c. **Misunderstanding of information about prescribed medications.**
d. **Cost.**
e. **Dys-mobiliy (arthritis, ..).**
f. **Social factors (living alone).**
g. **Dementia.**

Assessing and Monitoring Drug Therapy

1. **Compare the patient's problem list with drug list:**

A drug may be considered unnecessary if:

a. **It does NOT have indication per the problem list.**
b. **Is NOT effective.**
c. **The risk of its use outweighs the benefits.**
d. **There is therapeutic duplication.**

Assessing and Monitoring Drug Therapy

2. **Determine if the patient is having a chronic condition but is NOT receiving an evidence-based medication to improve outcome.**
3. **Monitor efficacy and toxicity of drugs by clinical assessment and lab tests.**

- **Examples:**

Amiodarone	**hepatic function tests**
Antiepileptics	**Drug level**
ACEi &ARBs	**Serum K^+ level**

Assessing and Monitoring Drug Therapy

Antipsychotics	**Extrapyramidal ADRs**
Diuretics	**Serum K^+ level**
Hypoglycemics	**Glucose and glycated Hb**
Lithium	**Serum level**
Warfarin	**PT or INR**
etc..	

Assessing and Monitoring Drug Therapy

4. **Documenting problems and formulating a therapeutic Plan:**

- **A reasonable clinical outcome for a 40-year-old patient may NOT be reasonable for an 80-year-old patient.**
- **Take into account: remaining life expectancy, time until therapeutic benefit, treatment target, medication regimen complexity and goals of care, when deciding on prescribing rationale.**

Assessing and Monitoring Drug Therapy

5. Implement a team-based management approach and develop strategies to avoid prescribing errors.
6. Take measures to enhance adherence to medications:

a. Modify medication schedule to fit patient's life-style.

b. Prescribe generic agents to reduce cost.

Assessing and Monitoring Drug Therapy

c. Offer easy-to-open bottles.
d. Offer easy-to-swallow dosage forms.
e. Provide both written and oral drug information.
f. Involve caregivers stressing the importance of adherence.

Assessing and Monitoring Drug Therapy

- **Assess the presence of drug-disease interactions:**

  Anticholinergics: benign prostatic hyperplasia & dementia or cognitive impairment.

  Antipsychotics: history of falls & Parkinson's disease.

  Aspirin: peptic ulcer disease.

  Calcium Channel blockers: heart failure.

  Metoclopramide: Parkinson's disease.

  NSAIDs: peptic ulcer disease, heart failure, renal failure.

Table 2. 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	Evidence
Anticholinergics					
First-generation antihistamines: Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Dimenhydrinate Diphenhydramine (oral) Doxylamine Hydroxyzine Meclizine Promethazine Triprolidine	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate	Avoid	Moderate	Strong	2015 Criteria: Duran 2013 Fox 2014 Kalisch Ellet 2014 From previous criteria: Agostini 2001 Boustani 2007 Guaiana 2010 Han 2001 Rudolph 2008
Antiparkinsonian agents Benztropine (oral) Trihexyphenidyl	Not recommended for prevention of extrapyramidal symptoms with antipsychotics; more-effective agents available for treatment of Parkinson disease	Avoid	Moderate	Strong	Rudolph 2008
Antispasmodics: Atropine (excludes ophthalmic) Belladonna alkaloids Clidinium-	Highly anticholinergic, uncertain effectiveness	Avoid	Moderate	Strong	Lechevallier-Michel 2005 Rudolph 2008

American Geriatric Society Beers Criteria for Potentially inappropriate medication Use in Older Adults

1. **Anticholinergics + other drugs with anticholinergic activity such as antihistamines:**

- **Rationale: elimination reduced in older adults.**
- **Risk: confusion, dry mouth, constipation, urine retention.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**

2. **Nitrofurantoin:**

- **Rationale: potential for pulmonary toxicity, hepatotoxicity, and peripheral neuropathy.**
- **Quality of evidence: low.**
- **Strength of recommendation: strong.**

3. **Peripheral and central α-blockers:**

- **Rationale: High risk of adverse effects, orthostatic hypotension, and CNS adverse effects.**
- **Quality of evidence: moderate - low.**
- **Strength of recommendation: strong.**

4. **Immediate-release nifedipine:**

- **Rationale: potential for hypotension and myocardial ischemia.**
- **Quality of evidence: high.**
- **Strength of recommendation: strong.**

5. **Amiodaraone:**

- **Rationale: High risk of many adverse effects.**
- **Quality of evidence: high.**
- **Strength of recommendation: strong.**

6. **Antidepressants:**

- **Rationale: highly anticholinergic, sedating, orthostatic hypotension and myocardial ischemia.**
- **Quality of evidence: high.**
- **Strength of recommendation: strong.**

7. **Antipsychotics:**

- **Rationale: increased risk of CVA, cognitive decline, dementia, and mortality.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**

7. **Barbiturates & benzodiazepines:**

- **Rationale: highly rate of dependence, tolerance, sedation, cognitive impairment, delirium, falls, fractures.**
- **Quality of evidence: high - moderate.**
- **Strength of recommendation: strong.**

8. **Insulin sliding scale (refers to the progressive increase in the pre-meal or night-time insulin dose, based on pre-defined blood glucose ranges):**

- **Rationale: increased risk of hypoglycemia.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**

9. **Long-acting sulfonylureas:**

- **Rationale: increased risk of hypoglycemia.**
- **Quality of evidence: high.**
- **Strength of recommendation: strong.**

10. **Metoclopramide:**

- **Rationale: increased risk of extrapyramidal adverse effects, dyskinesia.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**

11. Proton pump inhibitors:

- **Rationale: risk of *Clostridium difficile* infection.**
- **Quality of evidence: high.**
- **Strength of recommendation: strong.**

12. Meperidine (pethidine):

- **Rationale: high risk of neurotoxicity, including delirium.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**

13. NSAIDs:

- **Rationale: Increased risk of peptic ulcer disease, cardiovascular disease, renal failure.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**

14. Central muscle relaxants (chlorzoxazone, cyclobenzaprine, orphenadrine):

- **Rationale: poorly tolerated because of anticholinergic effects, sedation, increased risk of falls and fractures.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**