

Drug Use in the Elderly

Therapeutic Considerations in the Elderly:

- Elderly patients are those 65 years of age and older.
- Those who are > 65 years are NOT a one similar group.
- Institutionalized individuals are also different from those living in the community.
- Age-related changes in physiology can affect both the pharmacokinetics and the pharmacodynamics of drugs.
- 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.

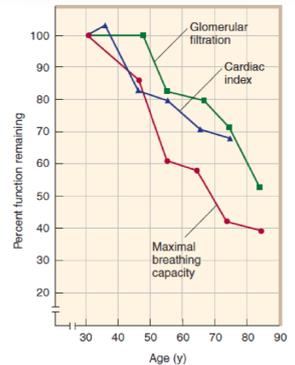


FIGURE 60-1 Effect of age on some physiologic functions. (Modified and reproduced, with permission, from Kohn RR: Principles of Mammalian Aging, Prentice-Hall, 1978.)

Note:
When the volume of distribution increase → plasma concentration decrease & vice versa
Volume distributions of lipid soluble drugs will increase
Drug-Protein binding → More free fraction of the drug in the elderly than young adults

Part of it; the muscles → low production of creatinine → result in erroneously normal creatinine
So, in elderly patient in one stage, serum creatinine is not good predictor of renal function

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) 18-20 (men)	38-45 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

when we say: "body water is less" = volume of distribution of water soluble drugs is less

Loading Dose =

$$\text{Therapeutic Drug Concentration} \times \text{Volume of Distribution}$$

Generally (with some exceptions), they require less doses than young adults.
reduced elimination of high extraction drugs (which are highly metabolised by the liver; becomes less metabolised)
metabolism is dependent on hepatic blood flow

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. → impairment of reflexes
 4. Increased vulnerability to disease.
 5. Frailty (weakness, fatigue, weight loss and functional decline). (ضعف وهشاشة)
- Individuals experience aging at different rates.

Common Physiological Changes Associated with Aging:

Include:

- a) Reduced functional reserve capacity.
- b) Reduced ability to maintain homeostasis, making them susceptible to de-compensation in stressful situations.

Impaired reflexes & adaptation = Not like young adults

Examples of such impaired homeostatic mechanisms:

- 1) Postural or gait instability
- 2) Orthostatic blood pressure responses
- 3) Thermoregulation impairment
- 4) Reduction of cognitive reserve
- 5) Bowel or bladder dysfunction.

السبب
↓
Dilatation of veins when you acquire the upright posture, failure of vasoconstriction & pooling of blood by gravity

→ During treatment of HTN we need drugs that don't affect sympathetic reflexes against postural HTN:
✓ sympathetic blockers
✓ Anti-hypertension + hypovolemia

Age-Related Altered Drug Pharmacokinetics:

Absorption:

- Absorption of drugs may be affected by age-related changes in GIT physiology, drug-food interactions, concurrent medication, and comorbidities affecting GI function.
- 1. The bioavailability of drugs absorbed by passive diffusion may not be affected significantly.
- Drugs absorbed by active transport (vitamin B12, calcium, iron, magnesium) may have impaired absorption.
- 2. First-pass effect is decreased, leading to an increase in bioavailability and plasma concentration of some drugs (propranolol, labetalol), while the bioavailability of some prodrugs is reduced (enalapril, codeine).
+ morphine → opioid has analgesic effect directly; but most of it is due to metabolism to morphine.
- 3. In the presence of atrophic gastritis, or in patients taking gastric acid-lowering agents, the extent of absorption of drugs requiring an acidic environment for absorption may be reduced (conazoles, iron, digoxin).

Distribution:

Water soluble → ↓
Fat soluble → ↑

↓
Reduction of blood flow, results in less codeine conversion to morphine, so it will produce at the same dose of young adults, less analgesia.

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 be influenced by ageing.
أكثر من النك passive
- The volume of distribution of water-soluble drugs (ethanol, gentamicin) 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.
 - 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.

Metabolism:

- Hepatic metabolism of drugs depends on liver perfusion, activity and capacity of drug metabolizing enzymes, and protein binding.
hepatic blood flow
↓ what will be metabolized is the free fraction of the drug
مقدار النك active
 - 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). → النك رايح
- Age-related decreases in hepatic blood flow (20-50%) can decrease significantly the metabolism of high extraction ratio drugs (propranolol, amitriptyline, diltiazem, lidocaine, metoprolol, morphine and verapamil).

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

estimated GFR → \leftarrow هاي المتعادلات بحسب الـ \leftarrow GFR or estimated creatinine clearance

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

→ 90Kg → Creatinine Clearance = 90
→ 1 → GFR = 125 ml/min
Creatinine production أقل ← أقل muscle mass الـ

تحت أقل

Multiply the result by 0.85 for females.

→ See this link for an update on renal function estimation:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5643354/pdf/11255_2017_Article_1682.pdf

نأخذ منها فكرة
لكن لازم نقول

Actual Measure
to adjust the
dose

- Accurate measurement of CL_{cr} is required for dose adjustment in patients with reduced renal function.
- Dosing guidelines of drugs that are eliminated by the kidney are based on creatinine clearance.
 - >> Some drugs should be avoided when CL_{cr} < 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, aminoglycosides, vancomycin.

we need to prevent the adverse effects: CL_{cr} reactions, in patients could have difficulty in hearing → If you use aminoglycosides 5 days or less, in general, patients are unlikely to develop hearing loss or nephrotoxicity

Age-Related Altered Drug Pharmacodynamics:

- Changes in PDs are less understood than changes in 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.

A. 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. → extra-pyramidal adverse reactions
- There is increased sensitivity to benzodiazepines, opioids, general anesthetics antipsychotics, lithium and anticholinergic drugs.

B. The elderly are more likely to develop orthostatic hypotension as an adverse effect of some antihypertensive drugs.

C. There is also:

- Increased hypotensive and bradycardic effect to calcium channel blockers.
- Reduced blood pressure response to β -blockers.
- Reduced effectiveness of diuretics. → إستنكس الـ loop diuretics بقدموا
- Increased risk of bleeding with warfarin. → to move to renal function على

the inside of the tubules to produce these effects.
→ high ceiling diuretics are exception

Drug-Related Problems in the Elderly:

Include 3 important, potentially preventable, negative outcomes:

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

Risk Factors:

→ at least 5 drugs

1. Polypharmacy including prescription and nonprescription drugs, herbal medicines, supplements and unnecessary drugs.

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

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. *****

Medication Problems Lecture
- self reading -

3. Underuse:

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

4. Medication non-adherence:

Causes:

→ should be reasonable to the life style of the patient.

- a. Adverse effects.
- b. Complex regimens.
- c. Misunderstanding of information about prescribed medications.
- d. Cost.
- e. Dys-mobility (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.

2. Determine if the patient is having a chronic condition but is NOT receiving an evidence-based medication to improve outcome.

3. Monitor effectiveness and toxicity of drugs by clinical assessment and lab tests.

• Examples:

Amiodarone	hepatic function tests
Antiepileptics	Drug level
ACEi & ARBs	Serum K ⁺ level → hyperkalemia هذو
Antipsychotics	Extrapyramidal ADRs
Diuretics	Serum K ⁺ level
Hypoglycemics	Glucose and glycated Hb
Lithium	Serum level
Warfarin	PT or INR
etc..	

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 rationally.

↳ Interfere with compliance & adherence to treatment

5. Implement a team-based management approach and develop strategies to avoid prescribing errors.

6. Take measures to enhance adherence to medications:

- Modify medication schedule to fit patient's lifestyle.
- Prescribe generic agents to reduce cost.
- Offer easy-to-open bottles.
- Offer easy-to-swallow dosage forms.
- Provide both written and oral drug information.
- Involve caregivers stressing the importance of adherence.

7. Assess the presence of drug-disease interaction:

Examples:

- Anticholinergics: benign prostatic hyperplasia & dementia or cognitive impairment.
- Antipsychotics: history of falls and Parkinson's disease.
- Aspirin: peptic ulcer disease.
- Calcium channel blockers: heart failure.
- Metoclopramide: Parkinson's disease.
- NSAIDs: peptic ulcer disease, heart failure and 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, Desbrompheniramine, Deschlorpheniramine Dimethylsulfonate, 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	Avoid	Moderate	Strong	2015 Criteria: Duran 2013, Fox 2014, Kalesch Ellet 2014 From previous criteria: Agostini 2001, Boustan 2007, Gansana 2010, Han 2001, Rudolph 2008
Antiparkinsonian agents, Benztropine (oral), Trihexyphenidyl	Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate				
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, Cnidium-	Highly anticholinergic, uncertain effectiveness	Avoid	Moderate	Strong	Lechevalier-Michel 2005, Rudolph 2008

Potentially Inappropriate Medication Use in Older Adults:

Risk: confusion, dry mouth, constipation, urine retention.

1. Anticholinergics

+ other drugs with anticholinergic activity such as antihistamines & antidepressants

2. Nitrofurantoin

potential for **lung Fibrosis**, hepatotoxicity, and peripheral neuropathy.

3. Peripheral and central α-blockers

High risk of adverse effects, orthostatic hypotension, and CNS adverse effects.

4. Immediate-release nifedipine

potential for hypotension and myocardial ischemia.
→ **Steal Syndrome** : ↓

5. Amiodaraone

High risk of many adverse effects.
Fibrosis / affect thyroid function (hypo/hyper) / liver

6. Antidepressants

highly anticholinergic, sedating, orthostatic hypotension and myocardial ischemia.

7. Antipsychotics

↳ **due to metabolic abnormalities (DM, hyperlipidemia)** increased risk of CVA, cognitive decline, & dementia, and mortality. **may lead to LND**

Rationale	Quality of evidence	Strength of recommendation
elimination reduced in older adults.	moderate.	✓ it depends on the severity of the proposed adverse reactions. → adverse effect dangerous strong.
potential for lung Fibrosis , hepatotoxicity, and peripheral neuropathy.	low.	✓ Pulmonary Fibrosis mortality rate is very high. strong.
High risk of adverse effects, orthostatic hypotension, and CNS adverse effects.	moderate - low.	✓ to avoid, because of severity. strong.
potential for hypotension and myocardial ischemia. → Steal Syndrome : ↓	high.	strong.
High risk of many adverse effects. Fibrosis / affect thyroid function (hypo/hyper) / liver	high.	strong.
highly anticholinergic, sedating, orthostatic hypotension and myocardial ischemia.	high.	strong.
↳ due to metabolic abnormalities (DM, hyperlipidemia) increased risk of CVA, cognitive decline, & dementia, and mortality. may lead to LND	moderate.	strong.

8. Barbiturates & benzodiazepines	highly rate of dependence, tolerance, sedation, cognitive impairment, delirium, falls, fractures.	high - moderate.	strong.
9. Insulin sliding scale (refers to the progressive increase in the pre-meal or nighttime insulin dose, based on pre-defined blood glucose ranges)	increased risk of hypoglycemia.	moderate.	strong.
10. Long-acting sulfonylureas	increased risk of hypoglycemia.	high.	strong.
11. Metoclopramide <i>very good antiemetic drug & GEAD</i>	increased risk of extrapyramidal adverse effects, dyskinesia.	moderate.	strong.
12. Proton pump inhibitors	risk of Clostridium difficile infection.	high.	strong.
13. Meperidine (pethidine)	high risk of neurotoxicity, including delirium.	moderate.	strong.
14. NSAIDs	Increased risk of peptic ulcer disease, cardiovascular disease, renal failure.	moderate.	strong.
15. Central muscle relaxants (chlorzoxazone, cyclobenzaprine, orphenadrine)	poorly tolerated because of anticholinergic effects, sedation, <u>increased risk of falls and fractures.</u>	moderate.	strong.

Done by: Ayat Nabil

