

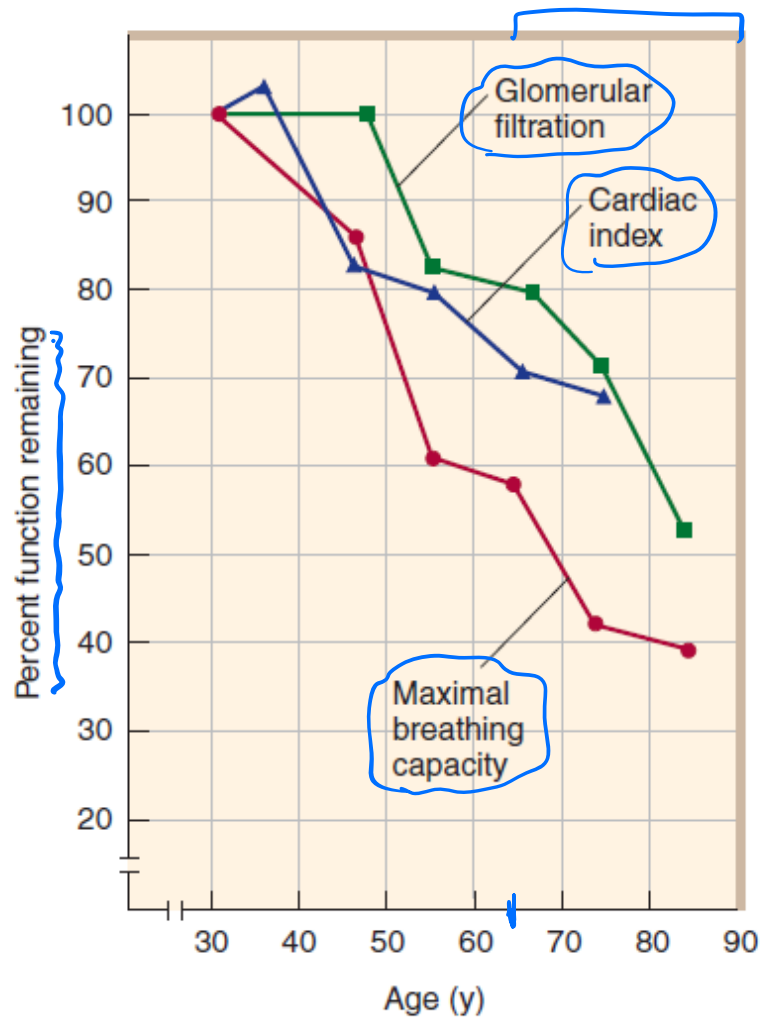
Drug Use in the Elderly

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Therapeutic Considerations in the Elderly

- Elderly patients are those 65 years of age and older.
maybe 55 y.o but bad health. (behavior of the body's function)
- 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.



normally,
healthy
aged
individual
will have
those.

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) 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	↓

↑ free fractions of drug.

↓ to 1/2 almost

especially the drugs

that will have 1st
pass effect.

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.


استعمال يفي للجور, smoker, CRC

Therapeutic Considerations in the Elderly

- The most common sensory impairments are difficulties in hearing and vision. *important especially in instructions.*
- 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.  reflexes
 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.

reflexes

Examples of such impaired homeostatic mechanisms:

- 1) Postural or gait ⁱⁿstability
- 2) Orthostatic blood pressure responses
- 3) Thermoregulation *e.g.: infection with mild fever*
- 4) Cognitive reserve
- 5) Bowel or bladder function. *e.g.: constipation, urinary retention, frequent UTIs (in BPH in males)*

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 co-morbidities affecting GI function.

Active + intact (unchanged) كمية الدواء التي بوصول الدم
1. The bioavailability of drugs absorbed by passive diffusion may not be affected significantly. Lipophilic drugs

- Drugs absorbed by active transport (vitamin B₁₂, calcium, iron, magnesium) may have impaired absorption.

• E.g.: 500 mg absorbed
400 mg reached the blood
∴ Bioavailability = 80%.

Age-Related Altered Drug Pharmacokinetics



Metabolism of the drug between intestinal mucosa and circulation

2. First-pass effect is decreased, leading to an increase in bioavailability and plasma concentration of some drugs (**propranolol**, *↓ doses are needed.* **labetolol**), while the bioavailability of some pro-drugs is reduced (**enalapril**, **codeine**). *↑ doses are needed.*
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**).
antacids, H₂ blockers, PPIs.
penicillin Abs
 - Acidic drugs will have disrupted absorption¹⁰ (they become ionized)

Age-Related Altered Drug Pharmacokinetics

Distribution: *protein binding*

*↓ Albumin
↓ water
↑ fat*

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.** *Thus drugs taken by muscle tissue like digoxin will become higher in plasma levels. (Proof is ↓ Creatinine production)*

4. **Reduced blood flow to tissues and organs.** *To assess the kidney function we test the Cr*

5. **Active uptake into tissues may be influenced by ageing.** *clearance not level.*

Age-Related Altered Drug Pharmacokinetics

- 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.

↳ This rule applies for drugs of long $t_{1/2}$ and used to treat critical illnesses.

• A drug with $t_{1/2}$?

• We need 4 $t_{1/2}$ to achieve steady state (therapeutic conc.).

Example • Digoxin $t_{1/2} = 36$ h.
for SVT, we cannot wait 4 days.

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:

1) Enzymes.

2) Perfusion

3) Protein binding.



∴



↓ metabolism in general.

- 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.

Age-Related Altered Drug Pharmacokinetics

- Drugs that undergo significant 1st pass effect → their clearance depends on the hepatic flow } normal metabolizing enzymes. ↓

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

- 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). → thus dose should be reduced.

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.

All drugs eliminated by the kidney will be higher in conc.
(↓ dose) proportion to the decrease in renal clearance.

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. *lower muscle mass in ♀*

➤ 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

Age-Related Altered Drug Pharmacokinetics

Actual not estimate.

- You should measure CL_{cr} accurately when you plan dose adjustment in patients with reduced renal function.
 - *To individualize the dose reduction according to the estimated 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 $CL_{cr} < 30$ mL/min: **colchicine**, **co-trimoxazole**, **glyburide**, **nitrofurantoin**, **probenecid**, **spironolactone**, **triamterene**.
 - for UTI* (pointing to co-trimoxazole)
 - Anti DM* (pointing to glyburide)
 - with penicillin + cephalosporins to ↑ their conc.* (pointing to nitrofurantoin)
 - K sparing diuretic.* (pointing to triamterene)
 - K sparing diuretic. in HF* (pointing to spironolactone)
 - ✓ Some drugs need **dose reduction** in reduced renal function: **acyclovir**, **amantadine**, **ciprofloxacin**, **gabapentin**, **ranitidine**.
 - anti herpes* (pointing to acyclovir)
 - anti-seizure* (pointing to gabapentin)
 - acid lowering agent.* (pointing to ranitidine)
- + Aminoglycoside Abs + Vancomycin.

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.**

Age-Related Altered Drug Pharmacodynamics

- 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. *like PD.*
 - 3. Drugs penetrate CNS easier than in young adults. *change in BBB.*

Age-Related Altered Drug Pharmacodynamics

- 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. ↑ response

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

→ In young adults → failure of venoconstriction
→ Reduced blood volume like: Hg₂, dehydration.

venodilatory drugs → Ortho. Hypo

All antihypertensive drugs can cause orthostatic/postural hypotension →
in the presence of dehydration or low blood volume.

} Elderly
↓ water
24
↓ veno-

Age-Related Altered Drug Pharmacodynamics

C. There is also:

- Increased hypotensive and bradycardic effect to calcium channel blockers.
- Reduced blood pressure response to β -blockers.
- Reduced effectiveness of diuretics. *bc they are dehydrated*
- 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 ^{Adverse Drug Rxns.} ADRs, risk of geriatric syndromes (falls, cognitive impairment), non-adherence, diminished functional status, and increased health care costs.

Drug-Related Problems in the Elderly

2. Inappropriate Prescribing, which includes:

- a. Wrong dose and duration. *No adjustment done*
- b. Duplication. *More than one doctor.*
- c. Drug interaction problem. *polypharmacy.*
- 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. *e.g.; Should be taken at midnight.*
- c. Misunderstanding of information about prescribed medications. *They require written instructions*
- d. Cost.
- e. Dys-mobility (arthritis, ..).
- f. Social factors (living alone).
- g. Dementia.

Duplication easy to repair.

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. ^① Monitor effectiveness and ^② toxicity of drugs by clinical assessment and lab tests.

- Examples:

Amiodarone

Anti-arrhythmic

hepatic function tests

+ TFT
bc it contains iodine.

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?!), depends on $t_{1/2}$ (till when it got to its therapeutic level) 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.
But bioequivalent

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

7. Assess the presence of drug-disease interaction:

Examples: *E.g: No anticholinergics (due to urinary retention)*

*↳ In BPH.
↳ In dementia.*

- a. Anticholinergics: benign prostatic hyperplasia & dementia or cognitive impairment.
- b. Antipsychotics: history of falls and Parkinson's disease.
- c. Aspirin: peptic ulcer disease.

Assessing and Monitoring Drug Therapy

d. Calcium channel blockers: heart failure.

Prokinetic agent + used to ↑ milk production

e. Metoclopramide: Parkinson's disease.

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

Na⁺ H₂O retention.

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 Benzotropine (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

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.
*UTI
Backache
to the Kidney*
 - Quality of evidence: moderate.
 - Strength of recommendation: strong.
- Sedating / H₁-blockers*

Potentially Inappropriate Medication Use in Older Adults

2. Nitrofurantoin: *UTI (especially in pregnancy)*
- Rationale: potential for pulmonary toxicity, hepatotoxicity, and peripheral neuropathy. *e.g. fibrosis*
 - Quality of evidence: low.
 - Strength of recommendation: strong.
Fibrosis is like a dead end.

Potentially Inappropriate Medication Use in Older Adults

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.

Potentially Inappropriate Medication Use in Older Adults

4. Immediate-release nifedipine: *can be given slow release **

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

angina pectoris, HF. (↓ O₂ requirements, ↑ blood flow)
Blue **steal** **syndrome**
↓

it dilates N blood vessels more than narrowed BVs ∴ blood diverts from ischemic area to normal area thus ↑ ischemia

heart. periphery

Potentially Inappropriate Medication Use in Older Adults

5. Amiodaraone:

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

Potentially Inappropriate Medication Use in Older Adults

6. Antidepressants:

- Rationale: highly anticholinergic, sedating, ^{*α-receptor blockers*} orthostatic hypotension and myocardial ischemia.
- Quality of evidence: high.
- Strength of recommendation: strong.

Potentially Inappropriate Medication Use in Older Adults

7. Antipsychotics:

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

Potentially Inappropriate Medication Use in Older Adults

8. Barbiturates & benzodiazepines:

~ long t_{1/2}!

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

Potentially Inappropriate Medication Use in Older Adults

9. 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.

Potentially Inappropriate Medication Use in Older Adults

10. ^{→ ↑ t_{1/2}} Long-acting sulfonylureas:
- ^{prolonged ↓} Rationale: increased risk of hypoglycemia.
 - Quality of evidence: high.
 - Strength of recommendation: strong.

Potentially Inappropriate Medication Use in Older Adults

11. Metoclopramide:

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

Potentially Inappropriate Medication Use in Older Adults

12. Proton pump inhibitors:
- Rationale: risk of Clostridium difficile infection.
 - Quality of evidence: high.
 - Strength of recommendation: strong.

not bc of ↓ absorption of
antacid drugs.

(fatal) pseudomembranous colitis

Anaerobic

bc they can abolish your
acid secretion for
24 hours.

Potentially Inappropriate Medication Use in Older Adults

13. Meperidine (pethidine):[†] *Opioids (Respiratory depression).*

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

Potentially Inappropriate Medication Use in Older Adults

14. NSAIDs:

- Rationale: Increased risk of peptic ulcer disease, ^{*Na⁺ H₂O retention + cardiotoxicity.*} cardiovascular disease, renal failure.
- Quality of evidence: moderate.
- Strength of recommendation: strong.

Potentially Inappropriate Medication Use in Older Adults

15. Central muscle relaxants (chlorzoxazone, cyclobenzaprine, orphenadrine): ^{+BD2}

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