GERIATRICS PHARMACOLOGY

Lancaster General Health Geriatrics Fellowship Conference

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Learning Objectives

1. Describe age-related alterations in pharmacokinetics and pharmacodynamics
2. Assess the risk of adverse drug events, drug–drug interactions, and drug–disease interactions in older adults, with consideration of pharmacokinetic and pharmacodynamic changes
3. Determine key considerations in geriatric pharmacotherapy through the evaluation of patient-specific clinical scenarios

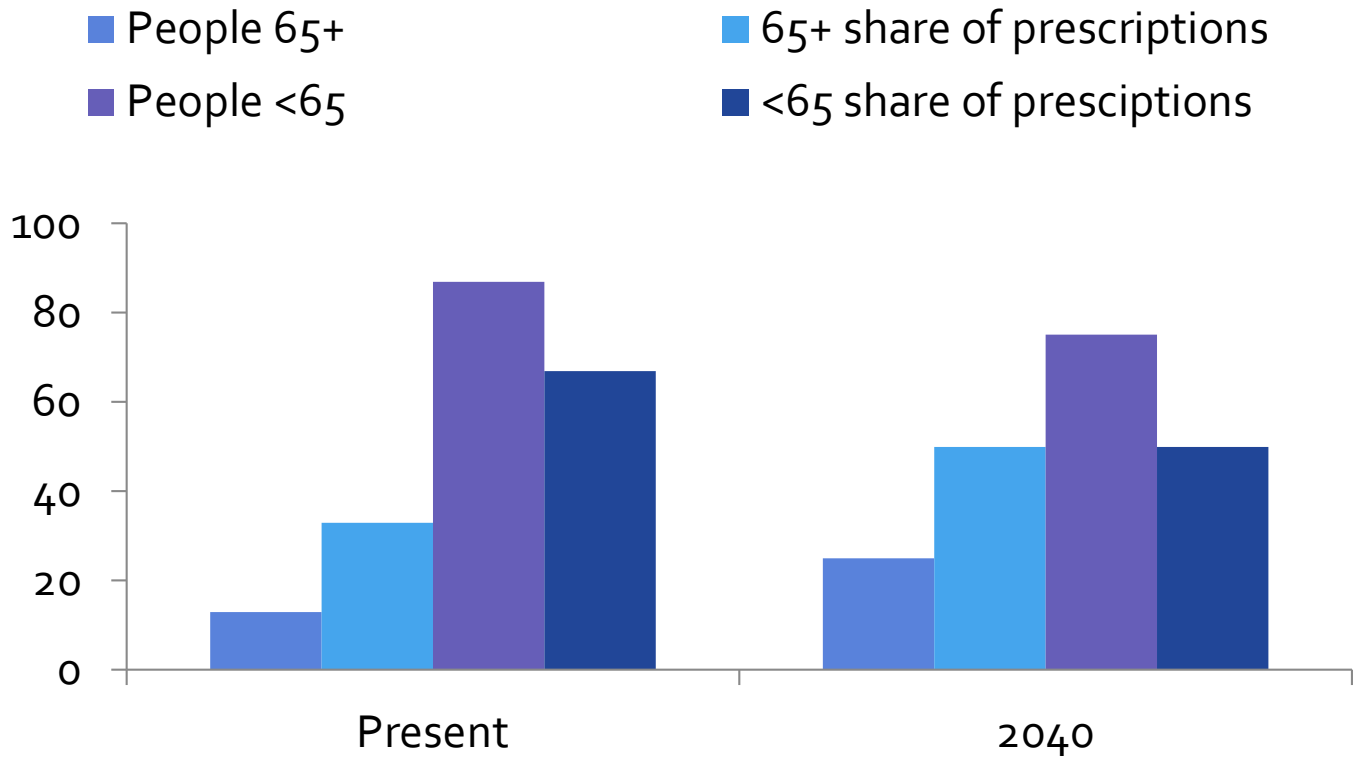
Question

Older adults are at higher risk of the following drug related problems:

A. Adverse drug events
B. Drug-drug interactions
C. Increased healthcare utilization

Why do we care?

- Our patient population and specialty
- The aging population is continuing to grow



Currently highest proportion of medications prescribed in relation to the United States Population

Responsible for 33% of all prescription drugs

Expected to increase by 50% by 2040

BJCP British Journal of Clinical Pharmacology

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Geriatric pharmacology and pharmacotherapy education for health professionals and students: a systematic review

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The rate of medication errors is high, and these errors can cause adverse drug reactions. Elderly individuals are most vulnerable to adverse drug reactions.
- One cause of medication errors is the lack of drug knowledge on the part of different health professionals.
- Medical curricula have changed in recent years, resulting in less education in the basic sciences, such as pharmacology.

AIMS

Given the reported high rates of medication errors, especially in elderly patients, we hypothesized that current curricula do not devote enough time to the teaching of geriatric pharmacology. This review explores the quantity and nature of geriatric pharmacology education in undergraduate and postgraduate curricula for health professionals.

METHODS

Pubmed, Embase and PsycINFO databases were searched (from 1 January 2000 to 11 January 2011), using the terms 'pharmacology' and 'education' in combination. Articles describing content or evaluation of

WHAT THIS STUDY ADDS

- Our study shows that little curricular time is devoted to geriatric pharmacology and that educational programmes in geriatric pharmacology have not been thoroughly evaluated.
- While interest in pharmacology education has increased recently, this is not the case for geriatric pharmacology education.
- Education on geriatric pharmacology should have more attention in the curricula of health professionals, given the often complex pharmacotherapy in elderly patients.
- Educational topics should be related to the known risk factors of medication errors, such as polypharmacy, dose adjustments in organ dysfunction and psychopharmacotherapeutics.

Table 1

Time spent on education in general pharmacology and geriatric pharmacology for different health professionals and students

Health professional	Articles (*n*) General pharm educ	Geriatric pharm educ	General pharmacology education* Education time median h (range)	Geriatric pharmacology education* Education time median h (range)
Undergraduate				
Medical student	61	12	80 (1.5–4956)	1.5 (1–23)
Pharmacy student	85	13	20 (1–400)	10 (1–160)
Nursing student	16	2	13 (1.25–85)	NA
Paramedical student	2	NA	20	NA
Dental student	1	NA	20	NA
Nurse practitioner student	1	1	NA	NA
Postgraduate				
Physician	47	11	8 (0.5–160)	2 (1.25–23)
Pharmacist	21	2	20 (0.25–935)	471 (7–935)
Nurse	25	NA	15 (0.25–304)	NA
Physician assistant	1	NA	3	NA
Nurse aractitioner	1	NA	3	NA
Other paramedical health professional	2	NA	38	NA
Total†	263	41	24 (0.25–4965)	2 (1–935)

*Eighty-nine articles lacked a description of the education time and were left out of the calculations. †Eleven articles had descriptions of education for more than one health professional. NA, data not available. The proportion to the total study load could not be calculated due to a lack of data on total study load in the majority of studies.

Why else should we care about older adults & medications?

- More drugs are available each year
- FDA and off-label indications are expanding
- Formularies change frequently
- Scientific advances in the understanding of drug-drug interactions
- Drugs change from prescription to OTC
- "Nutriceuticals" (herbal preparations, nutritional supplements) are booming
- Different pharmacokinetics/pharmacodynamics principles

PHARMACOKINETICS

Body's affect on the drug

"the time course of a drug and its metabolites through the body with respect to absorption, distribution, metabolism, and elimination"

ADME

With the many changes with aging…how does drug disposition and action change?

Pharmacokinetic Parameters to Review:

❶ **Absorption** from the gastrointestinal tract and other routes

❷ **Distribution** within the body: impact of body composition and protein binding

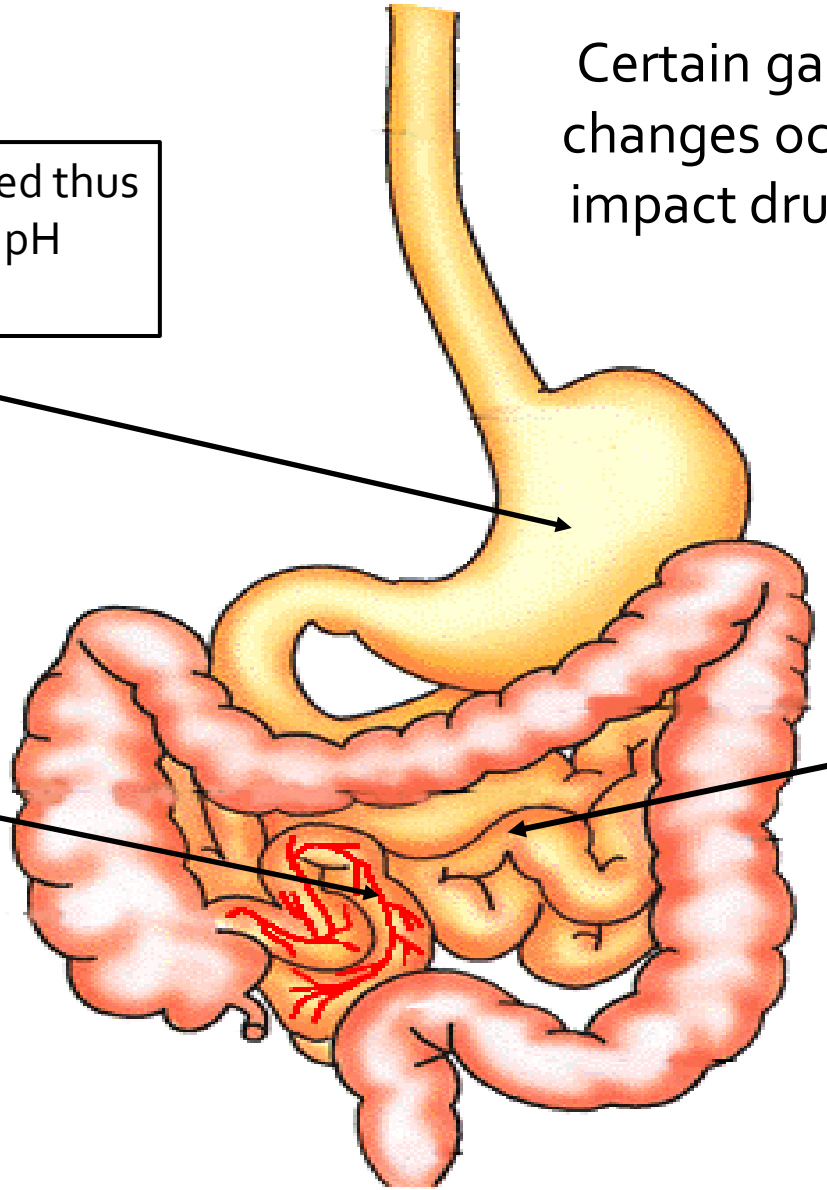
❸ **Metabolism** as a route of elimination

❹ **Excretion** as a route of elimination

ABSORPTION

Certain gastrointestinal changes occur which can impact drug absorption.

Gastric secretions are reduced thus we see an **INCREASE** in pH

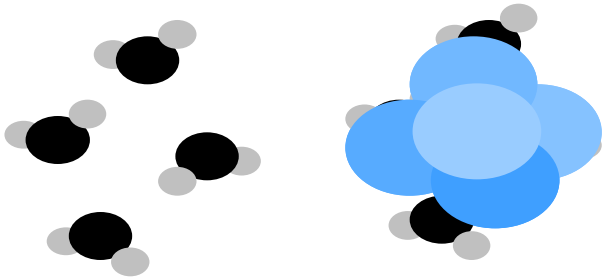


DECREASE in GI blood flow

DECREASE in GI motility

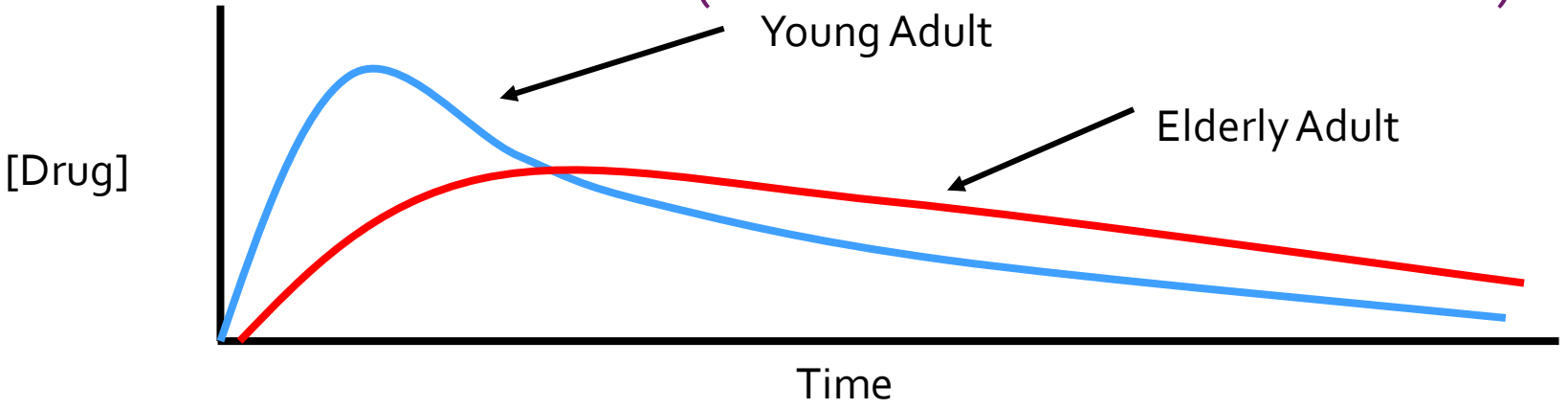
These changes can impact…

The dissolution of drugs caused by changes in pH



Calcium CARBONATE vs. CITRATE

or slow the absorption rate of drugs because of a reduction in GI blood flow and transit time (and thus slower onset of action).



- Amount absorbed (bioavailability) is not changed, but absorption may be slowed
- Peak serum concentrations may be lower and delayed

Other Absorption Considerations

Divalent cations (calcium, magnesium, iron) can affect absorption of many fluoroquinolones (eg, ciprofloxacin)

Enteral feedings interfere with absorption of some drugs (eg, phenytoin, levothyroxine)

Increased gastric pH may ***increase*** or ***decrease*** absorption of some drugs

Drugs that affect GI motility can affect absorption by decreasing the time spent in the GI tract

Inhibition or induction of GI tract enzymes by other medications

Thin skin and reduced blood flow to dermal layer can decrease absorption of topical agents

DISTRIBUTION

Changes in Volume of Distribution with Aging

Vd (L/Kg): locations in the body a drug penetrates and the time required for the drug to reach those locations

- Total Body Fat

- Total Body Water
- Lean Body Mass
- Albumin

They are ***drier***

- Less water – "chronically dehydrated" – normal with aging
- Lower volume of distribution, higher serum concentration of water soluble drugs
- Shorter half-lives
- Result can be increased side effects due to increased serum concentrations
- Examples: atenolol, alcohol, lithium

They are *fatter*

- Less lean muscle mass, higher % fat
- Higher volume of distribution
- Lower serum concentration of fat soluble drugs
- Longer half-lives
- Examples: benzodiazepines, propranolol, trazodone, vitamin D, statins

Changes in Protein Binding

Albumin (acidic drugs)

- Frail or malnourished older adults may have lower levels of albumin
- Increased *free* concentration of protein bound drugs
  - Levothyroxine, digoxin, aspirin, phenytoin

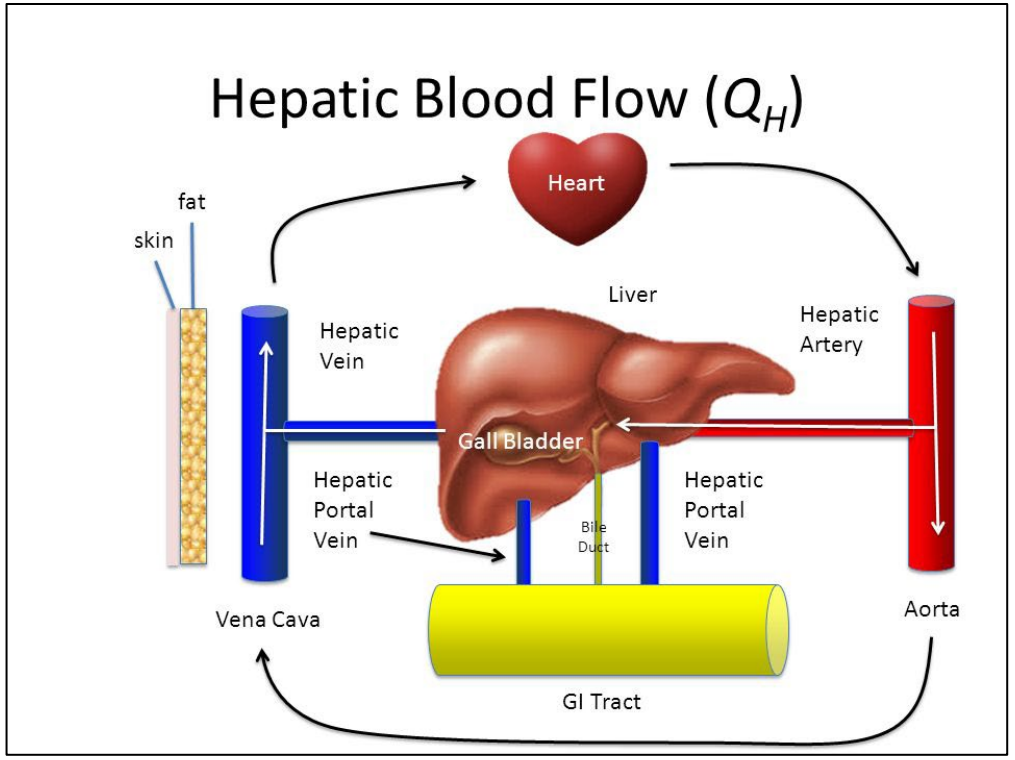
Vd Summary In Aging

- Age-associated changes in body composition can alter drug distribution
  - Distribution refers to the locations in the body a drug penetrates and the time required for the drug to reach these levels; expressed as the volume of distribution (Vd)
- ↓ body water → lower Vd for hydrophilic drugs (eg, Ethanol, lithium)
- ↓ lean body mass → lower Vd for drugs that bind to muscle (eg, Digoxin)
- ↑ fat stores → higher Vd for lipophilic drugs (eg, Diazepam, trazodone)
- ↓ plasma protein (albumin) → higher percentage of drug that is unbound (active)

METABOLISM

Changes to the Liver with Aging

- Liver plays a large role in drug metabolism
- Decrease in hepatic blood flow
  - 0.5-1% per year after age 25 → 40-45% for those 65+
- Liver volume decreases by 30%
- Decrease in number and function of CYP450 enzymes



Changes in Hepatic Metabolism with Aging

- ***Phase I pathways*** (eg, hydroxylation, oxidation, dealkylation, and reduction) convert drugs to metabolites with ***lesser, equal, or greater*** pharmacologic effect than parent compound
  - Potentially accumulating metabolites

- ***Phase II pathways*** convert drugs to inactive metabolites that do not accumulate
  - No change in phase 2 metabolism

With few exceptions, drugs metabolized by phase II pathways are preferred for older patients because they are not affected by aging.

Cytochrome P-450

- Effects of aging and clinical implications are still being researched
- CYP3A4 is involved in more than 50% of drugs on the market
- In vivo age- and gender-related reductions in drug clearance have been found for CYP3A4 substrates
- CYP3A4 is:
  - Induced by rifampin, phenytoin, and carbamazepine
  - Inhibited by macrolide antibiotics, itraconazole, ketoconazole, and grapefruit juice
- CYP2D6 is involved in the metabolism of 25%-30% of marketed medications
  - Associated with only minimal age-related changes
- CYP2D6 is involved in metabolism of many psychotropic drugs, and can be inhibited by many agents
- Some people are poor metabolizers (PMs) (10% of Caucasians); PMs >70 have serum concentrations 8-fold those of PMs <40

Other Factors Affecting Metabolism

- **Age and gender** (Zolpidem's peak serum concentrations and exposure have been reported to be 44.6% and 40.4% greater in older women, respectively, with only modest differences found between older and younger men)
- **Hepatic congestion from heart failure** (eg, reduces metabolism of warfarin)
- **Smoking** (eg, increases clearance of theophylline)

ELIMINATION

Half-life: time it takes for drugs plasma or serum concentration to decline by 50%

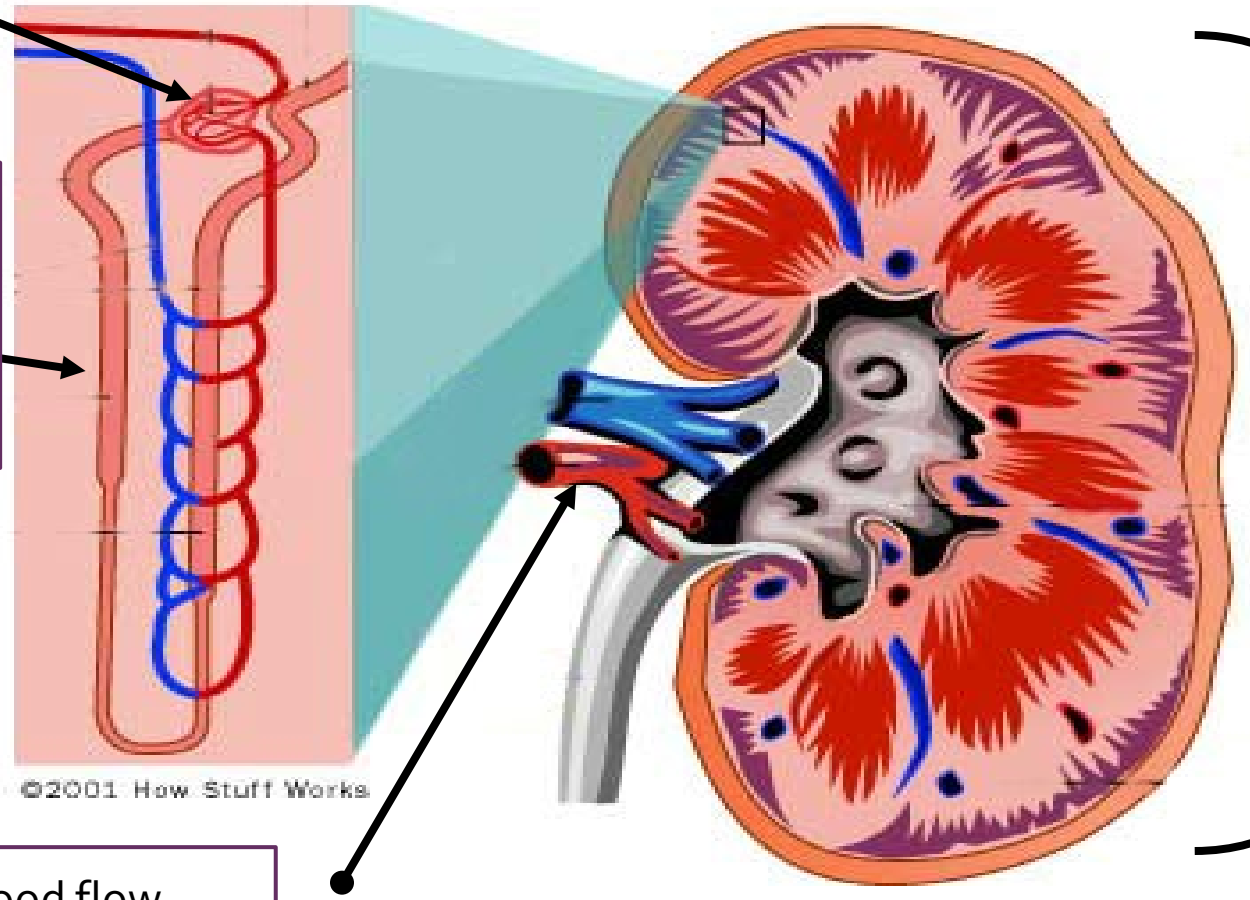
Steady state: amount of drug entering circulation = amount being eliminated

Clearance: volume of plasma or serum from which the drug is removed per unit of time

The number and function of nephrons in the kidney decreases with age.

GFR
can DECREASE up to 50%

DECREASED
reabsorption and trouble maintaining fluid and electrolyte status



Kidney size
DECREASES
10-40%

Renal blood flow
DECREASES 40-50%

Renal Elimination

- CrCl and GFR decrease with the aging process
- SCr may appear normal due to decrease in lean body mass, as there is lower creatinine production
- Important to review CrCl and not rely solely on the SCr as a marker of kidney function

Considered the pharmacokinetic parameter **MOST** affected by the aging process!

ESTIMATING RENAL FUNCTION AND DRUG DOSING DECISIONS

GFR vs. CrCl

Measuring Renal Function

- Most dosing references use Cockcroft and Gault equation to guide renal dosing (creatinine clearance)
- MDRD was created to define categories of chronic kidney disease (GFR)
- Considerations:

1. When to calculate CrCl? Does it work in acute situations?
2. Should we round SCr to 0.8 or 1.0 (when less than 0.8-1.0) in the Cockcroft and Gault equation?
3. Should we use GFR as an alternative to CrCl?

Comparison of Renal Estimation Equations for Drug Dosing

- Cockcroft-Gault
  - Gold standard over the years for renal drug dosing
    - Developed in 1976 and validated in at least 58 studies
  - Most utilized in package insert renal dosing recommendations

  - **Limitations**
    - Studied in CKD (not AKI); unstandardized SCr
    - Various recommendations for rounding of SCr in elderly and selection of weight for obese
    - Tends to underestimate clearance in elderly

- eGFR (MDRD / CKD-EPI)
  - Newer estimation of renal function for drug dosing
  - More common the past 10 years to be selected by manufacturers for renal dosing and renal cut offs for use
    - Examples: Sitagliptin (Januvia), Empagliflozin (Jardiance), Baricitinib, Remdesivir
  - Package inserts do not note which eGFR equation is used

  - **Limitations**
    - Studied in stable CKD (not AKI)
    - Normalized for BSA – need to consider in extremes of body weight for drug dosing
    - Variation between equations for higher clearance
    - Not validated in adults ≥85 years old or in racial or ethnic groups other than white and black Americans

Clin Biochem Rev. 2011 May; 32: 81-87
CKD & Drug Dosing: Information for Providers NIDDK March 2021 www.niddk.nih.gov
Adapted from Walls, J

Which Equation Should Be Used for Drug Dosing?

- Refer to the package insert for the method utilized (Cockcroft Gault vs eGFR)

- National Institute of Diabetes and Digestive Kidney Diseases (NIDDK):
  - Supports use Cockcroft Gault or eGFR (MDRD / CKD-EPI)
  - If using eGFR, "de-normalizing" for extremes of body weight
    - eGFR (ml/min) for drug dosing = eGFR (ml/min/1.73m^2) x BSA/1.73

- Be careful to account for creatinine trending and baseline function in overall assessment for renal dosing decisions especially at break points for adjustment

CKD & Drug Dosing: Information for Providers NIDDK March 2021 www.niddk.nih.gov
Adapted from Walls, J

Renal Dysfunction

IBW = Ideal body weight:
Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet
Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet

AjBW = adjusted body weight:
AjBW = IBW + 0.4(ABW - IBW)

- Cockcroft-Gault equation used to determine CrCl cutoffs for drug dosing

$$CrCl = \frac{(140 - age) \times weight}{72 \times SCr} \ (\times 0.85 \ if \ female)$$

- Techniques to prevent "as accurate" of a CrCl in an older adult
  - Use IBW
  - If underweight, use ABW
  - If ≥30% over IBW, use AdjBW ($IBW + 0.4[ABW\text{-}IBW]$)
  - Calculate CrCl for both IBW and ABW to get range
  - *+/- if SCr <1.0, round up to 1.0*
  - EPIC: use **.crcl**

Cystatin C

- Changes in muscle mass
- Smoking
- Diet (protein, keto, vegetarian)
- Illness (malnourished, cancer, CHF)
- Medications (steroids, ABX)

Kidney Int. 2024 Apr;105(4S):S117-S314.

Table 8| Indications for use of cystatin C

Domain	Specific clinical condition	Cause of decreased accuracy	Comments on GFR evaluation
Body habitus and changes in muscle mass	Eating disorders[127]	Non-GFR determinants of SCr	eGFRcys may be appropriate if no comorbid illness other than reduction in muscle mass.
	Extreme sport/exercise/ body builder	Non-GFR determinants of SCr	eGFRcys may be appropriate if an increase in muscle mass is the only abnormality.
	Above-knee amputation[128]	Non-GFR determinants of SCr	eGFRcys may be appropriate in those without other comorbid conditions. Suggest eGFRcr-cys in those with comorbid illness.
	Spinal cord injury with paraplegia/paraparesis or quadriplegia/quadriparesis	Non-GFR determinants of SCr	eGFRcys may be appropriate in those without other comorbid illness. Suggest eGFRcr-cys in those with comorbid illness.
	Class III obesity[a,b]	Non-GFR determinants of SCr and SCys	eGFRcr-cys demonstrated to be most accurate.
Lifestyle	Smoking[129-131]	Non-GFR determinants of SCys	Minimal data, suggest eGFRcr if no changes to non-GFR determinants of SCr or comorbid illness.
Diet	Low-protein diet	Non-GFR determinants of SCr	
	Keto diets	Non-GFR determinants of SCr	Minimal data, suggest eGFRcr may be appropriate if no changes to non-GFR determinants of SCr or no comorbid illness.
	Vegetarian	Non-GFR determinants of SCr	
	High-protein diets and creatine supplements	Non-GFR determinants of SCr	
Illness other than CKD	Malnutrition	Chronic illness, presumed impact on non-GFR determinants of SCr and SCys	eGFRcr-cys may be less accurate because of coexistence of malnutrition and inflammation. Suggest using mGFR for treatment decisions based on the level of GFR.
	Cancer[a,132-137]	Chronic illness, presumed impact on non-GFR determinants of SCr and SCys	eGFRcr-cys demonstrated to be most accurate in populations studied but likelihood of lesser accuracy in more frail people or in cancers with high cell turnover. Suggest using mGFR for treatment decisions based on the level of GFR.
	Heart failure[a,138,139]	Chronic illness, presumed impact on non-GFR determinants of SCr and SCys	Although limited data, eGFRcys appears less biased but all have low accuracy. Suggest using eGFRcr-cys or eGFRcys for routine GFR evaluation. Suggest using mGFR for treatment decisions based on the level of GFR.
	Cirrhosis[a,79,140,141]	Chronic illness, presumed impact on non-GFR determinants of SCr and SCys	Although limited data, eGFRcys appears less biased but all have low accuracy. Suggest using eGFRcr-cys or eGFRcys for routine GFR evaluation. Suggest using mGFR for treatment decisions based on the level of GFR.
	Catabolic consuming diseases[c]	Chronic illness, presumed impact on non-GFR determinants of SCr and SCys	Minimal data but eGFRcr-cys may be inaccurate. Suggest using eGFRcr-cys vs. eGFRcr for routine GFR evaluation. Suggest using mGFR for treatment decisions based on the level of GFR.
	Muscle wasting diseases[142]	Chronic illness, presumed impact on non-GFR determinants of SCr and SCys	Minimal data. One study shows large bias for both eGFRcr and eGFRcys. Suggest using eGFRcr-cys for routine GFR evaluation. Suggest using mGFR for treatment decisions based on the level of GFR.
Medication effects	Steroids (anabolic, hormone)	Non-GFR determinants of SCr. Effect on SCys not known	Physiological effect on SCys unknown, suggest eGFRcr-cys.
	Decreases in tubular secretion	Non-GFR determinants of SCr	eGFRcys may be appropriate if medication affects only creatinine and no comorbid illness. Suggest using mGFR for treatment decisions based on the level of GFR.
	Broad spectrum antibiotics that decrease extrarenal elimination	Non-GFR determinants of SCr	eGFRcys may be appropriate if medication affects only creatinine and no comorbid illness. Suggest using mGFR for treatment decisions based on the level of GFR.

Examples of Renally Cleared Medications

Noted in the Beers Criteria

TABLE 5. 2023 American Geriatrics Society Beers Criteria® for Medications That Should Be Avoided or Have Their Dosage Reduced with Varying Levels of Kidney Function in Older Adults

Drug	CrCl (mL/min) at Which Action Required	***Recommendation,*** Rationale, *Quality of Evidence (QE), Strength of Recommendation (SR)*
Anti-infective		
Ciprofloxacin	<30	***Doses used to treat common infections typically require reduction when CrCl <30 mL/min*** Increased risk of CNS effects (eg, seizures, confusion) and tendon rupture *QE = Moderate; SR = Strong*
Nitrofurantoin	<30	***Avoid if CrCl < 30mL/min*** Potential for pulmonary toxicity, hepatoxicity, and peripheral neuropathy, especially with long-term use. (See also Table 1.) *QE = Low; SR = Strong*
Trimethoprim-sulfamethoxazole	<30	***Reduce dosage if CrCl 15–29 mL/min. Avoid if CrCl <15 mL/min.*** Increased risk of worsening of kidney function and hyperkalemia; risk of hyperkalemia especially prominent with concurrent use of an ACE, ARB, or ARNI. *QE = Moderate; SR = Strong*
Cardiovascular and antithrombotics		
Amiloride	<30	***Avoid*** Hyperkalemia and hyponatremia *QE = Moderate; SR = Strong*
Dabigatran	<30	***Avoid when CrCl <30mL/min; dose adjustment advised when CrCl >30 mL/min in the presence of drug-drug interactions.*** Lack of evidence for efficacy and safety in individuals with a CrCl <30 mL/min. Label dose for patients with CrCl 15–30 mL/min based on pharmacokinetic data. *QE = Moderate; SR = Strong*

J Am Geriatr Soc. 2023 Jul;71(7):2052-2081.

Table 5 Continued

Drug	CrCl (mL/min) at Which Action Required	Rationale
Dofetilide	<60	***Reduce dose if CrCl 20–59 mL/min. Avoid if CrCl <20 mL/min.*** QTc prolongation and torsades de pointes. *QE = Moderate; SR = Strong*
Edoxaban	15–50 <15 or >95	***Reduce dose if CrCl 15–50 mL/min. Avoid if CrCl <15 or >95 mL/min.*** Lack of evidence of efficacy or safety in patients with a CrCl <30 mL/min *QE = Moderate; SR = Strong*
Enoxaparin	<30	***Reduce dose*** Increased risk of bleeding *QE = Moderate; SR = Strong*
Fondaparinux	<30	***Avoid*** Increased risk of bleeding *QE = Moderate; SR = Strong*
Rivaroxaban	<50	***Avoid if CrCl <15 mL/min. Reduce dose if CrCl 15–50 mL/min following manufacturer dosing recommendations based on indication-specific dosing.*** Lack of efficacy or safety evidence in people with CrCl <15 mL/min; limited evidence for CrCl 15–30 mL/min. *QE = Moderate; SR = Strong*
Spironolactone	<30	***Avoid*** Hyperkalemia *QE = Moderate; SR = Strong*
Triamterene	<30	***Avoid*** Hyperkalemia and hyponatremia *QE = Moderate; SR = Strong*
Central nervous system and analgesics		
Baclofen	eGFR <60	***Avoid baclofen in older adults with impaired kidney function (eGFR <60 mL/min). When baclofen cannot be avoided, use the lowest effective dose and monitor for signs of CNS toxicity, including altered mental status.*** Increased risk of encephalopathy requiring hospitalization in older adults with eGFR <60 mL/min or who require chronic dialysis. *QE = Moderate; SR = Strong*
Duloxetine	<30	***Avoid*** Increased GI adverse effects (nausea, diarrhea) *QE = Moderate; SR = Weak*

This table is not a comprehensive list of all drugs that should be avoided or dose-adjusted in older adults with renal impairment.

[a]NSAIDs include: Non-selective: diclofenac, diflunisal, etodolac, flurbiprofen, ibuprofen, indomethacin, ketorolac, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac; COX-2 selective: celecoxib; Nonacetylated salicylates: diflunisal, magnesium salicylate. This list does not include NSAIDs rarely or never used in the U.S. among older adults.

Table 5 Continued

Drug	CrCl (mL/min) at Which Action Required	Rationale
Gabapentin	<60	***Reduce dose*** CNS adverse effects *QE = Moderate; SR = Strong*
Levetiracetam	≤80	***Reduce dose*** CNS adverse effects *QE = Moderate; SR = Strong*
NSAIDs (non-selective, COX-2 selective, and nonacetylated salicylates, oral and parenteral)[a]	< 30	***Avoid*** May increase risk of acute kidney injury and further decline of kidney function *QE = Moderate; SR = Strong*
Pregabalin	<60	***Reduce dose*** CNS adverse effects *QE = Moderate; SR = Strong*
Tramadol	<30	***Immediate release: Reduce dose. Extended release. avoid*** CNS adverse effects *QE = Low; SR = Weak*
Gastrointestinal		
Cimetidine	<50	***Reduce dose*** Mental status changes *QE = Moderate; SR = Strong*
Famotidine	<50	***Reduce dose*** Mental status changes *QE = Moderate; SR = Strong*
Nizatidine	<50	***Reduce dose*** Mental status changes *QE = Moderate; SR = Strong*
Hyperuricemia		
Colchicine	<30	***Reduce dose; monitor for adverse effects*** GI, neuromuscular, bone marrow toxicity *QE = Moderate; SR = Strong*
Probenecid	<30	***Avoid*** Loss of effectiveness *QE = Moderate; SR = Strong*

Abbreviations for all Tables:

ACEIs=angiotensin-converting enzyme inhibitors; AChEI=acetylcholinesterase inhibitor; ARBs=angiotensin receptor blockers; ARNIs=angiotensin receptor-neprilysin Inhibitors; CCBs=calcium channel blockers; CNS=central nervous system COPD=chronic obstructive pulmonary disease; COX=cyclooxygenase; CrCl=creatinine clearance; CV=cardiovascular; DOACs=direct oral anticoagulants; GI=gastrointestinal; HFrEF=heart failure with reduced ejection fraction; HRT=hormone replacement therapy; INR=international normalized ratio; NSAIDs=nonsteroidal anti-inflammatory drugs; NYHA=New York Heart Association; RAS=renin-angiotensin system; SIADH= syndrome of inappropriate antidiuretic hormone secretion; SGLT2=sodium glucose co-transporter-2; SNRIs=serotonin-norepinephrine reuptake inhibitors; SSRIs=selective serotonin reuptake inhibitors; TCAs=tricyclic antidepressants; VTE=venous thromboembolism

J Am Geriatr Soc. 2023 Jul;71(7):2052-2081.

Patient Scenarios

Patient 1	Patient 2	Patient 3
82 year old female Patient with uncontrolled diabetes currently on metformin monotherapy. A1c 10.5% GFR 50, CrCl 33 mL/min Metformin okay? Added SGLT-2 inhibitor? GLP-1 agonist? Insulin?		

Patient Scenarios

Patient 1	Patient 2	Patient 3
82 year old female Patient with uncontrolled diabetes currently on metformin monotherapy. A1c 10.5% GFR 50, CrCl 33 mL/min Metformin okay? Added SGLT-2 inhibitor? GLP-1 agonist? Insulin?	79 year old male Patient newly diagnosed with Afib. GFR 36, CrCl 30 mL/min, SCr 1.5 Xarelto, Eliquis, Pradaxa, vs Warfarin?	

Patient Scenarios

Patient 1	Patient 2	Patient 3
82 year old female Patient with uncontrolled diabetes currently on metformin monotherapy. A1c 10.5% GFR 50, CrCl 33 mL/min Metformin okay? Added SGLT-2 inhibitor? GLP-1 agonist? Insulin?	79 year old male Patient newly diagnosed with Afib. GFR 36, CrCl 30 mL/min, SCr 1.5 Xarelto, Eliquis, vs Warfarin?	80 year old male with T2DM, concerns with worsening neuropathy affecting his sleep GFR 38, CrCl 32 mL/min Which of the following medications would we want to consider for patient? Gabapentin Duloxetine Pregabalin Other

PHARMACODYNAMICS

Drug's affect on the body

Pharmacodynamic Sensitivity

- Older adults tend to be **more or less sensitive** to certain medications
  - Changes in receptor number, receptor sensitivity/affinity, and neurotransmitter concentration
- This typically translates into the need to start with lower doses
  - **"Start low, go slow"**
- May be less sensitive to beta blockers and beta agonists
- May be more sensitive to:
  - Benzodiazepines
  - Opioids
  - Anticholinergic medications
  - Anticoagulants

PK/PD Summary from GRS

Parameter	Age effect	Disease factor effect	Prescribing implications
Absorption	Rate and extent are usually unaffected	Achlorhydria, concurrent medications, tube feedings	Drug-drug and drug-food interactions are more likely to alter absorption
Distribution	Increase in fat:water ratio; decreased plasma protein, particularly albumin	Heart failure, ascites, and other conditions increase body water	Fat-soluble drugs have a larger volume of distribution; highly protein-bound drugs have a greater (active) free concentration
Metabolism	Decrease in liver mass and liver blood flow decrease drug clearance; may be age-related changes in CYP2C19, while CYP3A4 and 2D6 are not affected	Smoking, genotype, other medications, alcohol, and caffeine have more effect than aging on metabolism	Lower dosages may be therapeutic
Elimination	Primarily renal; age-related decrease in glomerular filtration rate	Acute and/or chronic kidney impairment, decreased muscle mass can result in worse kidney function than serum creatinine (Cr) levels might suggest	Serum Cr not a reliable measure of kidney function; best to estimate Cr clearance using formula
Pharmacodynamics	Less predictable and often altered drug response at usual or lower concentrations	Drug-drug and drug-disease interactions may alter responses	Prolonged pain relief with opioids at lower dosages; more sedation and postural instability from benzodiazepines; altered sensitivity to β-blockers

OTHER CONCERNS

Adverse Drug Reactions

Drug-Drug Interactions

Drug-Disease Interactions

Adverse Drug Events (ADEs):

"an injury resulting from the use of a drug"

- More likely to occur in older adults
- Higher risk in the elderly due to changes in PK and PD, polypharmacy, non-adherence, and self-medication
- ADEs can result in hospitalization and functional decline
  - 5-28% of acute geriatric medical admissions
  - **Incidence of ADEs in hospitals: 26/1000 beds (2.6%)**
- Presentation of ADEs differs in older adults and is more likely to include geriatric syndromes such as memory loss, constipation, urinary incontinence, and falls

Risk Factors for ADEs in Older Adults

Age >85 years
Low Body Weight or BMI
6+ Concurrent Chronic Diagnoses
Estimated CrCl <50 mL/min
9+ Medications (Polypharmacy)
12+ Doses of Medications per day
Prior ADE

ADE Prescribing Cascade

Any new symptoms in an older adult is considered to be related to a drug until proven otherwise! Avoid the prescribing cascade!

Drug 1

Adverse drug effect—
misinterpreted as a new medical condition

Drug 2

Adverse drug effect—
misinterpreted as a new medical condition

Some other food for thought regarding ADEs

- In nursing homes, $1.33 is spent on ADEs for every $1.00 spent on medications
- ADE rate 50.1 per 1,000 person-years (preventable ADE rate 13.8)
- Cardiovascular drugs, diuretics, NSAIDs, hypoglycemics, and anticoagulants
- Most ADEs (≥95%) are considered predictable

Drug Interactions (DDI):

"pharmacologic or clinical response to the administration of a drug combination that differs from the anticipated from the known effects of each of the two agents when given alone"

- Can lead to ADEs and likelihood of DDI increases as numbers of medications increases
- Most common DDI leading to ADEs: neuropsychologic (delirium), artieral hypotension, acute kidney injury
- Changes in absorption
- Drugs with similar or opposite effects may result in exaggerated or impaired effects
- Drug metabolism - CYP interactions
- Risk factors: polypharmacy, several prescribers, multiple pharmacies

Examples from the Beers Criteria

TABLE 4. 2023 American Geriatrics Society Beers Criteria® for Potentially Clinically Important Drug–Drug Interactions That Should Be Avoided in Older Adults

Object Drug or Class	Interacting Drug or Class	***Recommendation,*** Risk Rationale, *Quality of Evidence (QE[a]), Strength of Recommendation (SR[a])*
RAS inhibitor (ACEIs, ARBs, ARNIs, aliskiren) or potassium-sparing diuretics (amiloride, triamterene)	Another RAS inhibitor or potassium-sparing diuretic	***Avoid routinely using 2 or more RAS inhibitors, or a RAS inhibitor and potassium sparing diuretic, concurrently in those with chronic kidney disease Stage 3a or higher.*** Increased risk of hyperkalemia. *QE = Moderate; SR = Strong*
Opioids	Benzodiazepines	***Avoid*** Increased risk of overdose and adverse events. *QE = Moderate; SR = Strong*
Opioids	Gabapentin Pregabalin	***Avoid; exceptions are when transitioning from opioid therapy to gabapentin or pregabalin, or when using gabapentinoids to reduce opioid dose, although caution should be used in all circumstances.*** Increased risk of severe sedation-related adverse events, including respiratory depression and death. *QE = Moderate; SR = Strong*

Table 4 Continued

Object Drug or Class	Interacting Drug or Class	***Recommendation,*** Rationale, *Quality of Evidence (QE[a]), Strength of Recommendation (SR[a])*
Warfarin	Amiodarone Ciprofloxacin Macrolides (excluding azithromycin) Trimethoprim-sulfamethoxazole SSRIs	***Avoid when possible; if used together, monitor INR closely*** Increased risk of bleeding *QE = Moderate; SR = Strong*

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Examples from the Beers Criteria

Table 4 Continued

Object Drug or Class	Interacting Drug or Class	***Recommendation,*** Rationale, *Quality of Evidence (QE[a]), Strength of Recommendation (SR[a])*
Anticholinergic	Anticholinergic	***Avoid, minimize number of anticholinergic drugs**** Use of more than one medication with anticholinergic properties increases risk of cognitive decline, delirium, and falls or fractures. *QE = Moderate; SR = Strong*
Antiepileptics (including gabapentinoids) Antidepressants (TCAs, SSRIs, and SNRIs) Antipsychotics Benzodiazepines Nonbenzodiazepine benzodiazepine receptor agonist hypnotics (i.e., "Z-drugs") Opioids Skeletal muscle relaxants	Any combination of ≥3 of these CNS-active drugs	***Avoid concurrent use of ≥3 CNS-active drugs (among types as listed at left); minimize number of CNS-active drugs.*** Increased risk of falls and of fracture with the concurrent use of ≥3 CNS-active agents (antiepileptics including gabapentinoids, antidepressants, antipsychotics, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonist hypnotics, opioids, and skeletal muscle relaxants). *QE = High; SR = Strong*
Lithium	ACEIs ARBs ARNIs	***Avoid, monitor lithium concentrations*** Increased risk of lithium toxicity. *QE = Moderate; SR = Strong*
Lithium	Loop diuretics	***Avoid, monitor lithium concentrations*** Increased risk of lithium toxicity *QE = Moderate; SR = Strong*
Non-selective peripheral alpha-1 blockers[b]	Loop diuretics	***Avoid in older women, unless conditions warrant both drugs*** Increased risk of urinary incontinence in older women *QE = Moderate; SR = Strong*
Phenytoin	Trimethoprim-sulfamethoxazole	***Avoid*** Increased risk of phenytoin toxicity *QE = Moderate; SR = Strong*
Theophylline	Cimetidine	***Avoid*** Increased risk of theophylline toxicity *QE = Moderate; SR = Strong*
Theophylline	Ciprofloxacin	***Avoid*** Increased risk of theophylline toxicity *QE = Moderate; SR = Strong*

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Common Drug-Disease Interactions

- Obesity alters Vd of lipophilic drugs
- Ascites alters Vd of hydrophilic drugs
- Dementia may ↑ sensitivity, induce paradoxical reactions to drugs with CNS or anticholinergic activity
- Renal or hepatic impairment may impair detoxification and excretion of drugs

Examples from the Beers Criteria

TABLE 2. 2023 American Geriatrics Society Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults Due to Drug–Disease or Drug–Syndrome Interactions That May Exacerbate the Disease or Syndrome

Disease or Syndrome	Drug(s)[a]	***Recommendation,*** Rationale, *Quality of Evidence (QE[b]), Strength of Recommendation (SR[c])*
Cardiovascular		
Heart failure	Cilostazol Dextromethorphan-quinidine Nondihydropyridine calcium channel blockers (CCBs) ■ Diltiazem ■ Verapamil Dronedarone NSAIDs and COX-2 inhibitors Thiazolidinediones ■ Pioglitazone	***Avoid: Cilostazol, Dextromethorphan-quinidine. Avoid in heart failure with reduced ejection fraction: Nondihydropyridine calcium channel blockers (CCBs), Diltiazem, Verapamil. Use with caution in patients with heart failure who are asymptomatic; avoid in patients with symptomatic heart failure: Dronedarone, NSAIDs and COX-2 inhibitors, Thiazolidinediones, Pioglitazone.*** Potential to promote fluid retention and/or exacerbate heart failure (NSAIDs and COX-2 inhibitors, non-dihydropyridine CCBs, thiazolidinediones); potential to increase mortality in older adults with heart failure (cilostazol and dronedarone); concerns about QT prolongation (dextromethorphan-quinidine). Note: This is not a comprehensive list of medications to avoid in patients with heart failure. *QE = Cilostazol, dextromethorphan-quinidine, COX-2 inhibitors: Low. Non-dihydropyridine CCBs, NSAIDs: Moderate. Dronedarone, thiazolidenediones: High; SR = Strong*
Syncope	Antipsychotics (selected) ■ Chlorpromazine ■ Olanzapine Cholinesterase inhibitors (AChEIs) ■ Donepezil ■ Galantamine ■ Rivastigmine Non-selective peripheral alpha-1 blockers ■ Doxazosin ■ Prazosin ■ Terazosin Tertiary tricyclic antidepressants (TCAs) ■ Amitriptyline ■ Clomipramine ■ Doxepin ■ Imipramine	***Avoid*** Antipsychotics listed and tertiary TCAs increase the risk of orthostatic hypotension. AChEIs cause bradycardia and should be avoided in older adults whose syncope may be due to bradycardia. Non-selective peripheral alpha-1 blockers cause orthostatic blood pressure changes and should be avoided in older adults whose syncope may be due to orthostatic hypotension. *QE = High; SR = Antipsychotics, non-selective peripheral alpha-1 blockers: Weak. AChEIs, tertiary TCAs: Strong*

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MORE TO COME!

Optimal Prescribing

Principles of Prescribing

Deprescribing

Polypharmacy

Beers Criteria

Take Home Points

- The population of those ≥65 years old is continuing to rise
- With aging, psychologic, pharmacokinetic, and pharmacodynamic changes making older adults more prone to adverse drug events
  - Renal function is most effected!
  - "Start low and go slow"
- Older adults are at an increased risk of adverse drug events, drug interactions. This could also effect their current disease states.
  - Avoid the prescribing cascade!

PATIENT CASES

Let's Compare…

- Patient A is a 72 yo WF who lives at home with her husband and her dog.
- She wears glasses and has a hearing aid.
- She has a PMH of diabetes, hypothyroidism and HTN that are well controlled.
- She takes levothyroxine, metformin, atorvastatin, calcium, vitamin D, and lisinopril.
- She and her husband enjoy gardening, hiking, and traveling.

- Patient B is a 72 yo WF who lives at home with her husband and her dog.
- She wears glasses and has a hearing aid.
- She has a PMH of uncontrolled diabetes, peripheral neuropathy, CKD, hypothyroidism, history of hip fracture, history of falls, LE edema, obesity, and HTN.
- She takes levothyroxine, metformin, insulin, gabapentin, alendronate, calcium, vitamin D, lisinopril, furosemide, oxybutynin, and amlodipine.
- She ambulates with a rolling walker and enjoys playing board games.

Patient Case Discussion

- What do these two patients have in common?
- How are these two patients different?
- Which patient do you think is more likely to experience an adverse drug event and drug interactions? Why?
- What other concerns do you have for these individuals?

Let's Compare…

- Patient A is a 72 yo WF who lives at home with her husband and her dog.
- She wears glasses and has a hearing aid.
- She has a PMH of diabetes, hypothyroidism and HTN that are well controlled.
- She takes levothyroxine, metformin, atorvastatin, calcium, vitamin D, and lisinopril.
- She and her husband enjoy gardening, hiking, and traveling.

- Patient B is a 72 yo WF who lives at home with her husband and her dog.
- She wears glasses and has a hearing aid.
- She has a PMH of uncontrolled diabetes, peripheral neuropathy, CKD, hypothyroidism, history of hip fracture, history of falls, LE edema, obesity, and HTN.
- She takes levothyroxine, metformin, insulin, gabapentin, alendronate, calcium, vitamin D, lisinopril, furosemide, oxybutynin, and amlodipine.
- She ambulates with a rolling walker and enjoys playing board games.

Mr. Pharmacy, 84 YOM

- Presents for a complete medication review during his AWV
- Widowed, after his wife passed away 2 years ago and resides in independent living at a local CCRC

PMH	Medication	Sig
Atrial fibrillation	Digoxin 0.25 mg Warfarin 10 mg	1 PO qday 1 PO qday
Hypertension	Doxazosin 4mg Diltiazem CD 120 mg	1 PO qHS 1 PO qday
Allergic rhinitis	Diphenhydramine 25 mg	1 PO Every 12 hours PRN
Insomnia	Zolpidem 10 mg	1 PO QHS PRN sleep
Depression	Paroxetine 20 mg	1 PO QHS
Anxiety	Diazepam 2mg	1 PO BID
Osteopenia	Calcium carbonate 500 mg	1 PO BID with food

For Discussion

- Concerns for PK/PD changes (absorption, distribution, metabolism, elimination)
- Adverse Reactions
- Drug-Drug Interactions

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PMH	Medication	Concerns
Atrial fibrillation	Digoxin 0.25 mg Warfarin 10 mg	High dose → risk of toxicity High dose → risk of bleeding
Hypertension	Doxazosin 4mg Diltiazem CD 120 mg	Orthostatic Hypotension High extraction drug, bradycardia
Allergic rhinitis	Diphenhydramine 25 mg	Anticholinergic effects
Insomnia	Zolpidem 10 mg	Delirium, falls, fractures
Depression	Paroxetine 20 mg	Anticholinergic effects, sedation, orthostatic hypotension
Anxiety	Diazepam 2mg	Lipophilic → cognitive impairment, delirium , falls, fractures, car accidents
Osteopenia	Calcium carbonate 500 mg	Absorption

Extra Case (if time allots)

- Mrs. XYZ is an 85-year old female with PMH of orthostatic hypotension, urinary incontinence, reflux, CAD (MI with multiple stents in 2010), chronic pain, depression with anxiety, osteoporosis, and hypothyroidism. She presents for evaluation of recent cognitive decline.
- Recent BPs 102/62, 92/60, 86/54
- SCr 1.17, Wt 133 lb, Ht 65 in
- MoCA: 20/30 (-3 orientation, -1 registration, -3 recall, -1 repetition, -1 praxis, abnormal clock draw)
- Geriatric Depression Scale: 12/15
- Social/ADLs: needs help with bathing, uses cane or walker to ambulate, depends on family members for all IADLs

Mrs. XYZ's Medications

- Imdur 60 mg QAM & 120 mg QPM
- Amlodipine 2.5 mg daily
- Aspirin 81 mg daily
- Plavix 75 mg daily
- Midodrine 5 mg BID
- Synthroid 75 mcg daily
- Citalopram 40 mg daily
- Dexilant 60 mg BID
- Magnesium gluconate 400 mg BID
- Ranexa 1000 mg BID
- Vitamin D 2000 IU daily
- Miralax 17 gm daily
- Centrum Silver 1 tab daily
- Nitroglycerin 0.4 mg SL as needed (hasn't used since MI in 2010)
- Alprazolam 0.5 mg q8h PRN anxiety (using 1-2 tabs each day)
- Oxybutynin ER 10 mg every other day
- Prolia 60 mg SQ every 6 months
- Fentanyl 100 mcg q72h

PK/PD considerations? ADEs? Etc?

- Imdur 60 mg QAM & 120 mg QPM
- Amlodipine 2.5 mg daily
- Aspirin 81 mg daily
- Plavix 75 mg daily
- Midodrine 5 mg BID
- Synthroid 75 mcg daily
- Citalopram 40 mg daily
- Dexilant 60 mg BID
- Magnesium gluconate 400 mg BID
- Ranexa 1000 mg BID
- Vitamin D 2000 IU daily
- Miralax 17 gm daily
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GERIATRICS PHARMACOLOGY

Lancaster General Health Geriatrics Fellowship Conference

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