



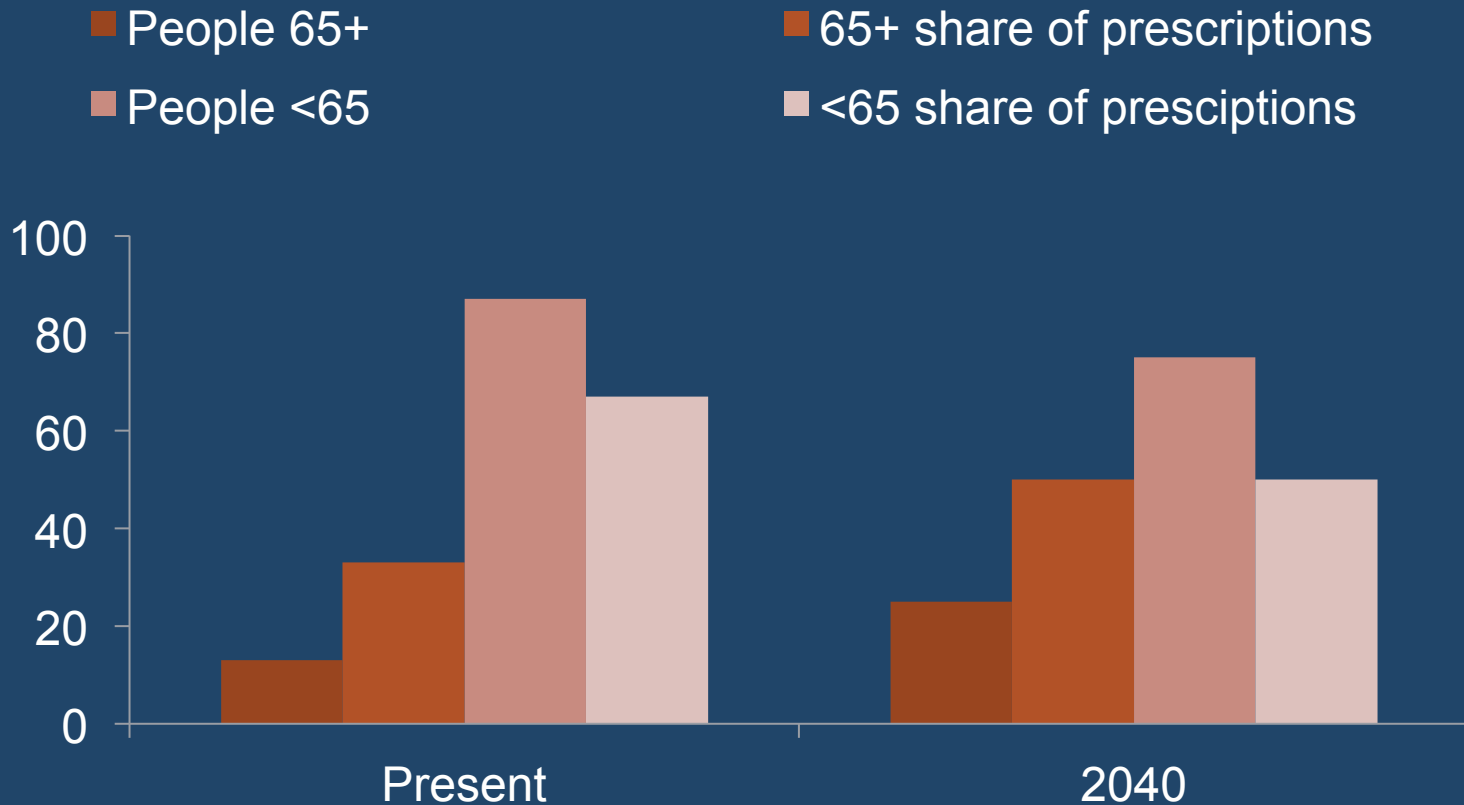
# PHARMACOTHERAPY

Know and understand:

- Key issues in geriatric pharmacology
- Effects of age on pharmacokinetics and pharmacodynamics
- Risk factors for adverse drug events for older patients and ways to mitigate them
- Principles of prescribing for older patients

- Challenges of Geriatric Pharmacology
- Age-Associated Changes in Pharmacokinetics
- Age-Associated Changes in Pharmacodynamics
- Optimizing Prescribing
- Adverse Drug Events
- Drug-drug and Drug-disease Interactions
- Principles of Prescribing for Older Adults
- Nonadherence

# WHY GERIATRIC PHARMACOTHERAPY IS IMPORTANT



Now, people age 65+ are 13% of US population, buy 33% of prescription drugs  
By 2040, will be 25% of population, will buy 50% of prescription drugs

# WHY GERIATRIC PHARMACOTHERAPY IS CHALLENGING

- 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

# AGE-ASSOCIATED CHANGES IN PHARMACOKINETICS

- Absorption
- Distribution
- Metabolism
- Elimination

- Amount absorbed (bioavailability) is not changed, but absorption may be slowed
- Peak serum concentrations may be lower and delayed
- **Exceptions: drugs with extensive first-pass effect** (bioavailability may increase and serum concentrations may be higher because less drug is extracted by the liver, which is smaller with reduced blood flow)

# FACTORS THAT AFFECT DRUG ABSORPTION (1 of 2)

- Route of administration
- What is taken with the drug
- Comorbid illnesses



# FACTORS THAT AFFECT DRUG ABSORPTION (2 of 2)

- 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

# EFFECTS OF AGING ON VOLUME OF DISTRIBUTION ( $V_d$ )

- 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 ( $V_d$ )
- ↓ body water → lower  $V_d$  for hydrophilic drugs (eg. Ethanol, lithium)
- ↓ lean body mass → lower  $V_d$  for drugs that bind to muscle (eg. Digoxin)
- ↑ fat stores → higher  $V_d$  for lipophilic drugs (eg. Diazepam, trazodone)
- ↓ plasma protein (albumin) → higher percentage of drug that is unbound (active)

The liver is the most common site of drug metabolism

Metabolic clearance of a drug by the liver may be reduced because:

- Aging decreases liver blood flow, size and mass
- Drug clearance is reduced for drugs subject to phase I pathways or reactions

# WHY THE METABOLIC PATHWAY MATTERS

- **Phase I pathways** (eg, hydroxylation, oxidation, dealkylation, and reduction) convert drugs to metabolites with  $<$ ,  $=$ , or  $>$  pharmacologic effect than parent compound
- **Phase II pathways** convert drugs to inactive metabolites that do not accumulate
  - With few exceptions, drugs metabolized by phase II pathways are preferred for older patients

- 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, nefazodone, 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 white people); PMs >70 have serum concentrations 8-fold those of PMs <40

# OTHER FACTORS THAT AFFECT DRUG METABOLISM

- **Age and gender** (eg, oxazepam is metabolized faster in older men than in older women; nefazodone concentrations are 50% higher in older women than in younger women)
- **Hepatic congestion from heart failure** (eg, reduces metabolism of warfarin)
- **Smoking** (eg, increases clearance of theophylline)

- **Half-life:** Time for serum concentration of drug to decline by 50%
- **Clearance:** Volume of serum from which the drug is removed per unit of time (eg, L/hour or mL/minute)



# KIDNEY FUNCTION IS CRITICAL FOR DRUG ELIMINATION

- Most drugs exit the body via the kidney
- Reduced elimination → drug accumulation and toxicity
- Aging and common geriatric disorders can impair kidney function

# THE EFFECTS OF AGING ON THE KIDNEY

↓ kidney size

↓ renal blood flow

↓ number of functioning nephrons

↓ renal tubular secretion

**Result: Decreased kidney function**

# SERUM CREATININE DOES NOT REFLECT CREATININE CLEARANCE

↓ lean body mass → lower creatinine production

*and*

↓ glomerular filtration rate (GFR)

**Result: In older people, serum creatinine stays in normal range, masking change in creatinine clearance (CrCl)**

# TWO WAYS TO DETERMINE CREATININE CLEARANCE

## Measure

- Time-consuming
- Requires 24-hour urine collection
- 8-hour collection may be accurate but not widely accepted

## Estimate

- Usually done with the Cockcroft-Gault equation  
(*see next slide*)

## COCKROFT-GAULT EQUATION

$$\frac{(\text{weight in kg}) (140 - \text{age})}{(72) (\text{stable serum creatinine in mg/dL})} \times (0.85 \text{ if female})$$

# LIMITATIONS OF THE COCKROFT-GAULT EQUATION

- In patients without a significant age-related decline in renal function, the equation underestimates CrCl
- In patients with muscle mass reduced beyond normal aging, the equation overestimates CrCl
- Modification of Diet in Renal Disease (MDRD) is another method for estimating GFR
  - Not validated in adults  $\geq 70$  years old or in racial or ethnic groups other than white and black Americans

- **Definition:** Time course and intensity of the pharmacologic effect of a drug
- **May change with aging, for example:**
  - Benzodiazepines may cause more sedation and poorer psychomotor performance in older adults (likely cause: reduced clearance of the drug and resultant higher plasma levels)
  - Older patients may experience longer pain relief with morphine

- Achieve balance between over- and underprescribing of beneficial therapies
- >20% of ambulatory older adults receive at least one potentially inappropriate medication
- Nearly 4% of office visits and 10% of hospital admissions result in prescription of medications classified as never or rarely appropriate



- Underprescribing can result from thinking that older adults will not benefit from:
  - Medications intended as primary or secondary prevention
  - Aggressive treatment of chronic conditions

# BEERS CRITERIA

- Intend to improve drug selection and reduce exposure to potentially inappropriate medications in older adults
- Recommendations are evidence-based and in 5 categories:
  - Drugs to avoid
  - Drugs to avoid in patients with specific diseases or syndromes
  - Drugs to use with caution
  - Selected drugs whose dose should be adjusted based on kidney function
  - Selected drug-drug interactions
- Available at AGS web site: [www.americangeriatrics.org](http://www.americangeriatrics.org)

# COMMONLY OVERPRESCRIBED AND INAPPROPRIATELY USED DRUGS

- Androgens/testosterone
- Anti-infective agents
- Anticholinergic agents
- Urinary & GI antispasmodics
- Antipsychotics
- Benzodiazepines
- Nonbenzodiazepine hypnotics
- Digoxin as first-line for afib or heart failure
- Dipyridamole
- H<sub>2</sub> receptor antagonists
- Insulin, sliding scale
- NSAIDs
- Proton-pump inhibitors
- Sedating antihistamines
- Skeletal muscle relaxants
- Tricyclic antidepressants

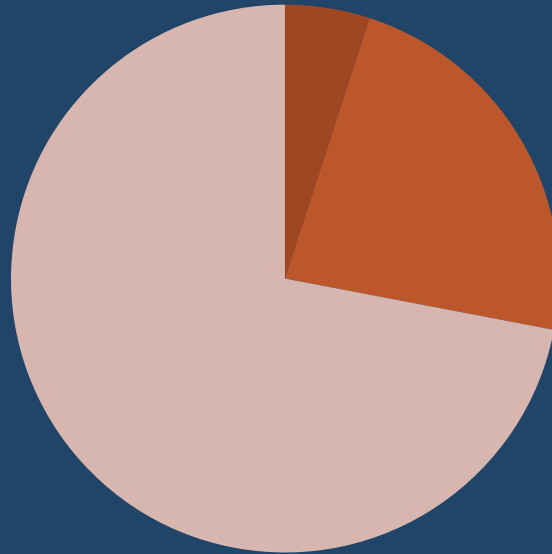
# COMMONLY UNDERPRESCRIBED DRUGS

- ACE inhibitors for patients with diabetes and proteinuria
- Angiotensin-receptor blockers
- Anticoagulants
- Antihypertensives and diuretics for uncontrolled hypertension
- $\beta$ -blockers for patients after MI or with heart failure
- Bronchodilators
- Proton-pump inhibitors or misoprostol for GI protection from NSAIDs
- Statins
- Vitamin D and calcium for patients with or at risk of osteoporosis

- An injury resulting from the use of a drug
- Adverse drug reaction (ADR): a type of ADE referring to harm directly caused by a drug at usual dosages

- 6 or more concurrent chronic conditions
- 12 or more doses of drugs/day
- 9 or more medications
- Prior adverse drug event
- Low body weight or low BMI
- Age 85 or older
- Estimated CrCl < 50 mL/min

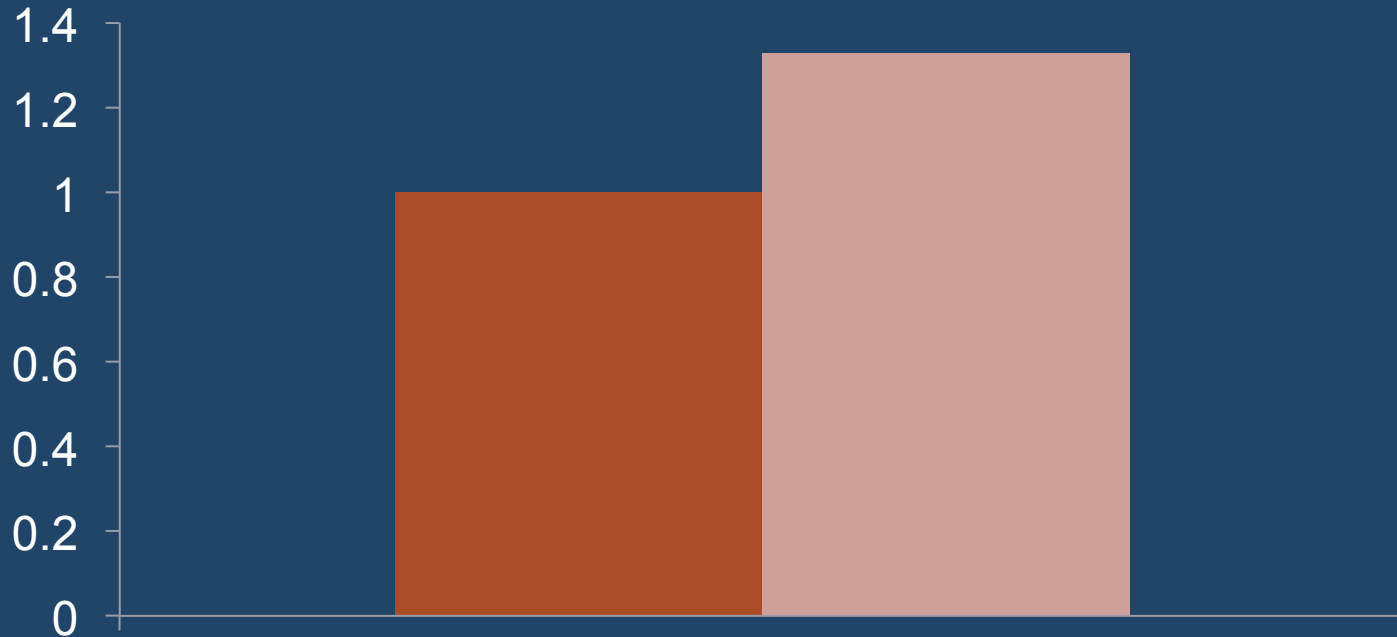
# THE BURDEN OF INJURIES FROM MEDICATIONS (1 of 2)



ADEs are responsible for 5% to 28% of acute geriatric medical admissions

Incidence of ADEs in hospitals: 26/1000 beds  
(2.6%)

# THE BURDEN OF INJURIES FROM MEDICATIONS (2 of 2)



In nursing homes, \$1.33 is spent on ADEs  
for every \$1.00 spent on medications




# ADEs IN THE AMBULATORY SETTING

- ADE rate 50.1 per 1,000 person-years (preventable ADE rate 13.8)
- Cardiovascular drugs, diuretics, NSAIDs, hypoglycemics, and anticoagulants
- Most ADEs ( $\geq 95\%$ ) are considered predictable


Drug 1




Adverse drug effect—  
misinterpreted as a new medical condition



Drug 2



Adverse drug effect—  
misinterpreted as a new medical condition



- May lead to ADEs
- Risk increases as number of medications increases
- Most common: cardiovascular and psychotropic drugs

# KEY FACTS ABOUT DRUG-DRUG INTERACTIONS

- Absorption can be  $\uparrow$  or  $\downarrow$
- Use of drugs with similar or opposite effects can result in exaggerated or diminished effects
- Drug metabolism may be inhibited or induced

# MOST COMMON ADVERSE EFFECTS OF DRUG-DRUG INTERACTIONS

- Neuropsychologic (primarily delirium)
- Arterial hypotension
- Acute kidney failure

# ADVERSE DRUG INTERACTIONS THAT INCREASE THE RISK OF HARM (1 of 3)

Combination	Risk
ACE inhibitor + potassium-sparing diuretic	Hyperkalemia
Anticholinergic + anticholinergic	Cognitive decline
Calcium channel blockers + erythromycin or clarithromycin	Hypotension and shock
Concurrent use of $\geq 3$ CNS active drugs	Falls and fractures
Digoxin + erythromycin, clarithromycin, or azithromycin	Digoxin toxicity
Lithium + loop diuretics or ACE inhibitor	Lithium toxicity

# ADVERSE DRUG INTERACTIONS THAT INCREASE THE RISK OF HARM (2 of 3)

Combination	Risk
Peripheral $\alpha_1$ blockers + loop diuretics	Urinary incontinence in women
Phenytoin + SMX/TMP	Phenytoin toxicity
Sulfonylureas + SMX/TMP, ciprofloxacin, levofloxacin, erythromycin, clarithromycin, azithromycin, and cephalixin	Hypoglycemia
Tamoxifen + paroxetine (other CYP2D6 inhibitors)	Prevention of converting tamoxifen to its active moiety, resulting in increased breast cancer-related deaths

# ADVERSE DRUG INTERACTIONS THAT INCREASE THE RISK OF HARM (3 of 3)

Combination	Risk
Theophylline + ciprofloxacin	Theophylline toxicity
Trimethoprim (alone or as SMX/TMP) + ACE inhibitor or ARB or spironolactone	Hyperkalemia
Warfarin + SMX/TMP, ciprofloxacin, levofloxacin, gatifloxacin, fluconazole, amoxicillin, cephalexin, and amiodarone	Bleeding
Warfarin + NSAIDs	GI bleeding



# COMMON DRUG-DISEASE INTERACTIONS

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

# PRINCIPLES OF PRESCRIBING FOR OLDER PATIENTS: THE BASICS

- Start with a low dose
- Titrate upward slowly, as tolerated by the patient
- Avoid starting 2 drugs at the same time

# BEFORE PRESCRIBING A NEW DRUG, CONSIDER:

- Is this medication necessary?
- What are the therapeutic end points?
- Do the benefits outweigh the risks?
- Is it used to treat effects of another drug?
- Could 1 drug be used to treat 2 conditions?
- Could it interact with diseases, other drugs?
- Does patient know what it's for, how to take it, and what ADEs to look for?

# PRINCIPLES OF PRESCRIBING ANNUALLY

- Ask patient to bring in all medications (prescribed, OTC, supplements) for review
- Ask about side effects and screen for drug and disease interactions
- Look for duplicate therapies or pharmacologic effect
- Eliminate unnecessary medications and simplify dosing regimens

- May be as high as 50% among older patients
- Predictors of nonadherence:
  - Asymptomatic disease
  - Inadequate follow-up
  - Patient's lack of insight of value of treatment
  - Missed appointments/transportation difficulties
  - Poor provider-patient relationship

- Interventions to improve drug compliance:
  - Medication reviews and counseling to identify barriers, simplify regimens, and provide education
  - Telephone call reminders
  - Reminder charts and calendars have been shown to be less effective
  - Interactive technology to supervise, remind, and monitor drug adherence (limited availability, has not undergone extensive scientific analysis)
  - Involve a caregiver
  - Utilize a medication tray

*Do not prescribe a medication without  
conducting a drug regimen review*

Based on the American Board of Internal Medicine Foundation's  
Choosing Wisely® Campaign

- Appropriate prescribing means choosing the correct dosage of the correct drug for the condition and individual patient
- Age alters pharmacokinetics (drug absorption, distribution, metabolism, and elimination)
- ADEs are common but can be minimized with strict attention to risk factors, drug-drug interactions, and drug-disease interactions



# CASE 1 (1 of 4)

- The husband of an 82-year-old woman calls because his wife's behavior has changed over the last few days.
- - She is confused and becomes agitated when he assists with ADLs.
  - She will not eat because she thinks she is being poisoned.
- History: hypertension, depression, osteoarthritis, probable Alzheimer disease (diagnosed 2 years ago), urinary incontinence
  - MMSE score was 22 of 30 at last visit 2 months ago.
- Medications: acetaminophen 325 mg four times daily, donepezil 5 mg/d, extended-release memantine 14 mg/d, hydrochlorothiazide 25 mg/d, lisinopril 10 mg/d, tolterodine 2 mg twice daily, and citalopram 20 mg/d
  - Donepezil and memantine were begun 2 years ago.
  - Tolterodine was increased 1 week ago.
  - Citalopram was increased (from 10 mg) 2 months ago.

- A visiting nurse obtains laboratory samples later that day.
- Laboratory findings:
  - Blood urea nitrogen 18 mg/dL
  - Serum creatinine 1.1 mg/dL
  - Sodium 138 mEq/L
  - Glucose 81 mg/dL (consistent with prior measurements)
  - Urinalysis 0–5 WBCs/hpf, negative for bacteria and leukocyte esterase

Which one of the following is most appropriate at this time?

- A. Discontinue tolterodine.
- B. Increase extended-release memantine to 28 mg/d.
- C. Start lorazepam 0.5 mg twice daily.
- D. Start risperidone 0.25 mg/d.

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## CASE 2 (1 of 4)

- An 80-year-old woman fell and underwent repair of hip fracture 3 days ago. She now reports dizziness, and the nurse notes excessive daytime drowsiness.
- History: hypertension, frequent falls, post-herpetic neuralgia
- Pre-admission medications have been restarted.
  - Hydrochlorothiazide 12.5 mg/d, extended-release metoprolol 50 mg/d, amlodipine 10 mg/d, gabapentin 600 mg three times daily, calcium carbonate 500 mg three times daily
- Medications started after surgery:
  - Subcutaneous enoxaparin 30 mg/d, daily multivitamin, docusate 250 mg twice daily, senna 8.6 mg twice daily
  - Oxycodone 5–15 mg every 4 hours as needed for pain; she received two 10-mg doses in the last 24 hours.

- Examination
  - Weight 45 kg (99 lb), blood pressure 144/76 mmHg, with no orthostatic changes
  - Estimated creatinine clearance (based on laboratory samples drawn today) is 30 mL/min.
    - ❖ Two months ago, estimated clearance was 60 mL/min.

Which one of the following is the best next step in management?

- A. Discontinue oxycodone.
- B. Increase enoxaparin to 30 mg twice daily.
- C. Reduce gabapentin to 600 mg twice daily.
- D. Start alendronate 70 mg once weekly.

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