PHARMACOTHERAPY
OBJECTIVES

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
TOPICS COVERED

• 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
AGING AND ABSORPTION

- 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
- 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 (Vd)

- 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)
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.
• **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)
Most drugs exit the body via the kidney

Reduced elimination $\rightarrow$ 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 Cockroft-Gault equation 
  *(see next slide)*
Cockroft-Gault Equation

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

- **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
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
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$_2$ 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
- β-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
ADVERSE DRUG EVENTS

- 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
RISK FACTORS FOR ADEs

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

Incidence of ADEs in hospitals: 26/1000 beds (2.6%)
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 (≥95%) are considered predictable
ADE PRESCRIBING CASCADE

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
• Absorption can be ↑ or ↓

• 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)

<table>
<thead>
<tr>
<th>Combination</th>
<th>Risk</th>
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</thead>
<tbody>
<tr>
<td>ACE inhibitor + potassium-sparing diuretic</td>
<td>Hyperkalemia</td>
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<tr>
<td>Anticholinergic + anticholinergic</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Calcium channel blockers + erythromycin or clarithromycin</td>
<td>Hypotension and shock</td>
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<tr>
<td>Concurrent use of $\geq 3$ CNS active drugs</td>
<td>Falls and fractures</td>
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<tr>
<td>Digoxin + erythromycin, clarithromycin, or azithromycin</td>
<td>Digoxin toxicity</td>
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<tr>
<td>Lithium + loop diuretics or ACE inhibitor</td>
<td>Lithium toxicity</td>
</tr>
<tr>
<td>Combination</td>
<td>Risk</td>
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<td>-------------------------------------------------</td>
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<tr>
<td>Peripheral alpha&lt;sub&gt;1&lt;/sub&gt; blockers + loop diuretics</td>
<td>Urinary incontinence in women</td>
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<tr>
<td>Phenytoin + SMX/TMP</td>
<td>Phenytoin toxicity</td>
</tr>
<tr>
<td>Sulfonylureas + SMX/TMP, ciprofloxacin, levofloxacin, erythromycin, clarithromycin, azithromycin, and cephalexin</td>
<td>Hypoglycemia</td>
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<tr>
<td>Tamoxifen + paroxetine (other CYP2D6 inhibitors)</td>
<td>Prevention of converting tamoxifen to its active moiety, resulting in increased breast cancer-related deaths</td>
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<tr>
<td>Combination</td>
<td>Risk</td>
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<td>----------------------------------------------------------------------------</td>
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<tr>
<td>Theophylline + ciprofloxacin</td>
<td>Theophylline toxicity</td>
</tr>
<tr>
<td>Trimethoprim (alone or as SMX/TMP) + ACE inhibitor or ARB or spironolactone</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Warfarin + SMX/TMP, ciprofloxacin, levofoxacin, gatifloxacin, fluconazole,</td>
<td>Bleeding</td>
</tr>
<tr>
<td>amoxicillin, cephalexin, and amiodarone</td>
<td></td>
</tr>
<tr>
<td>Warfarin + NSAIDs</td>
<td>GI bleeding</td>
</tr>
</tbody>
</table>
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
• 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?
• 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
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.
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.
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.
Which one of the following is the best next step in management?

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