PHARMACOTHERAPY IN THE OLDER PERSON

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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

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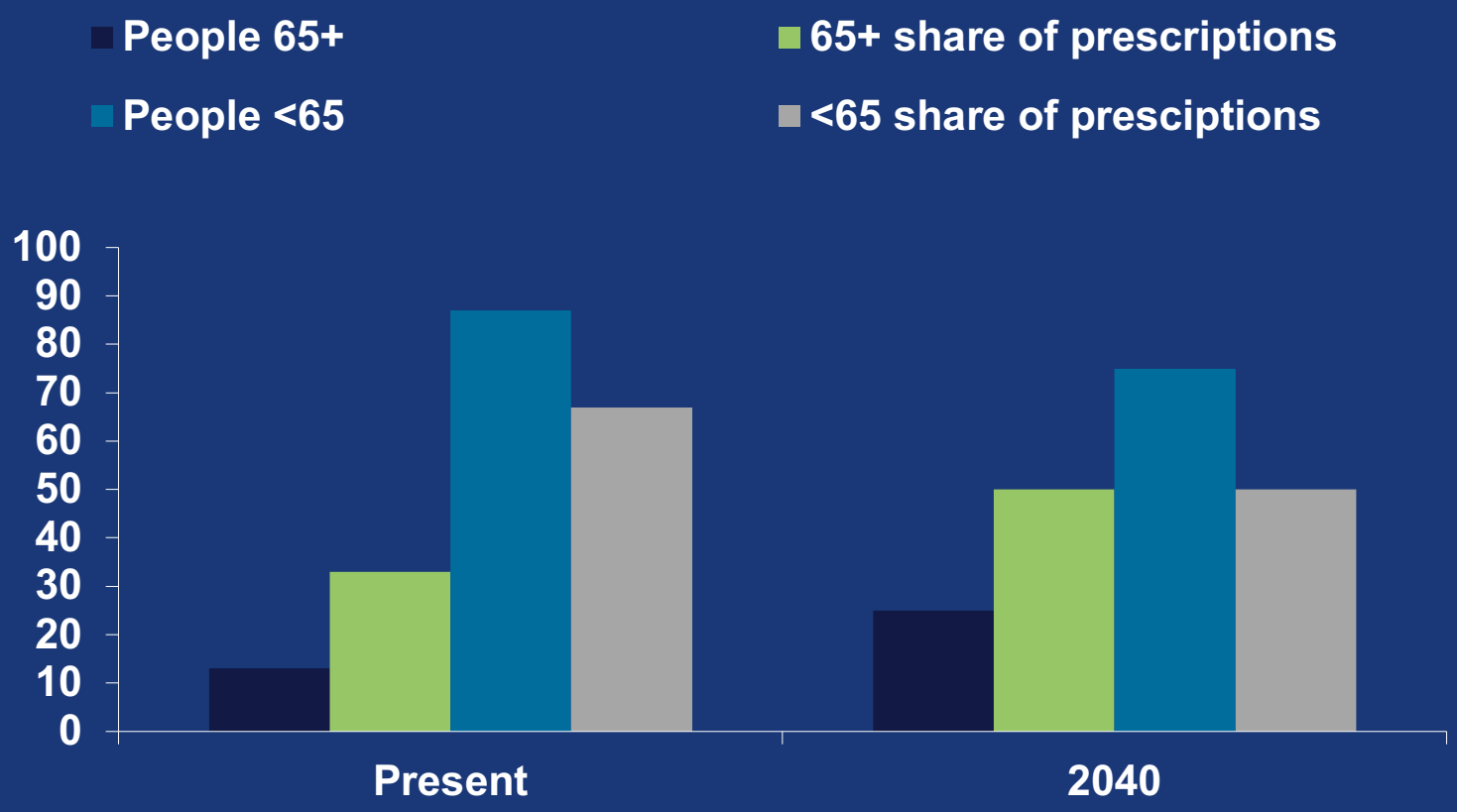
CASE PRESENTATION

- 96 year old gentleman, PMH of HTN, BPH, dementia and blindness seen for an urgent house call visit. Patient was able to walk and transfer with assistance 4 months ago. Since then complained of hallucination and sleep disturbance. Started on Haldol by PCP with resolution of hallucinations. For 4-6 weeks, no longer able to ambulate or transfer. Has difficulty swallowing with food pocketing, drooling and somnolence
- Medications: tolterodine ER 4mg daily, Flomax 0.4mg daily, haloperidol 2 mg qhs, Irbesartan 150mg daily, amlodipine 2.5mg daily, atorvastatin 20mg daily, vitamin D 2000IU daily, EC ASA 81mg daily
- PE: BP 86/55, pulse 49-68, temp 35.2 pulse ox 95% RA
- masked faces, rigidity with cogwheeling, able to make words but difficult to articulate, somnolent, rest negative

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

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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

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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

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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)

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METABOLISM

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

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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

CYTOCHROME P-450 (1 of 2)

- 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

CYTOCHROME P-450 (2 of 2)

- 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

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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)

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ELIMINATION

- 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 $\rightarrow$ drug accumulation and toxicity
- Aging and common geriatric disorders can impair kidney function

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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)

COCKROFT-GAULT EQUATION

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

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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 ≥70 years old or in racial or ethnic groups other than white and black Americans

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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

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OPTIMIZING PRESCRIBING (1 of 2)

- 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

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OPTIMIZING PRESCRIBING (2 of 2)

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

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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

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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

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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

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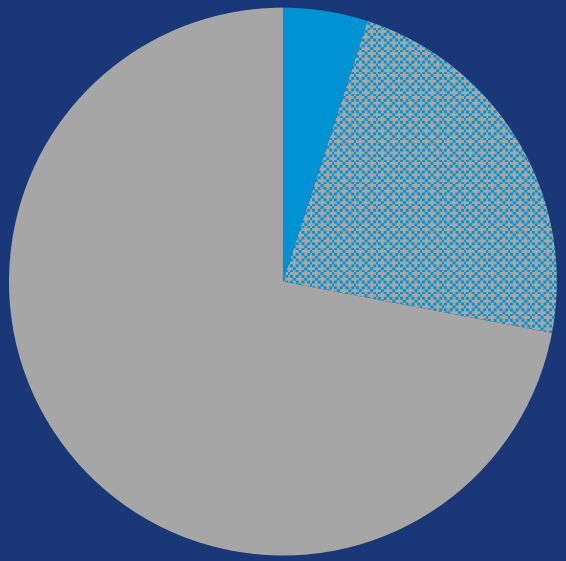
RISK FACTORS FOR ADEs

- 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

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 (≥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

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DRUG-DRUG INTERACTIONS

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

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KEY FACTS ABOUT DRUG-DRUG INTERACTIONS

- 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)

Combination	Risk
ACE inhibitor + potassium-sparing diuretic	Hyperkalemia
Anticholinergic + anticholinergic	Cognitive decline
Calcium channel blockers + erythromycin or clarithromycin	Hypotension and shock
Concurrent use of ≥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 cephalexin	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

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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

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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

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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?

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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

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NONADHERENCE (1 of 2)

- 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

NONADHERENCE (2 of 2)

- 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

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CHOOSING WISELY®

Do not prescribe a medication without conducting a drug regimen review

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

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SUMMARY

- 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

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