Key Issues, Challenges & Solutions in Geriatric Pharmacology

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DISCLOSURES
The presenters have no conflicts of interest.

LEARNING OBJECTIVES
- Describe key issues & challenges in geriatric pharmacology.
- Discuss the effects of age on pharmacokinetics and pharmacodynamics.
- Identify risk factors for adverse drug events for older patients and ways to mitigate them.
- Identify common drug interactions.
- Effectively apply the Beers criteria to a geriatric patient case scenario.
- Describe principles of rational prescribing for older patients.
OVERVIEW

• Case Presentation
• Polypharmacy & Related Challenges
• Beers Criteria - What, Why & How
• Summarize Challenges
• Considerations in “Rational Prescribing”
• Aging, Pharmacokinetics & Pharmacodynamics
• Application to Cases
• Q & A

A CASE...

› 78 year old frail appearing, petite female presents to your office seeking care after moving to your community.
› Patient has not had a primary care provider for years
› Her care has been provided by 6 specialists
› Her need today is a refill all of her medications
› Does not bring any current progress notes or medical record but tells you her medical problems
› She gives you her medications in a small suitcase...
› Daughter-in-law in room but is not aware of patient’s history

Patient’s Medication List

› Morphine ER 15mg
› Morphine ER 30mg
› Morphine IR 15mg
› Cimetidine 400mg
› Advair HFA 230-21
› Carvedilol 3.125mg
› Atorvastatin 40mg
› Aspirin 81mg
› Albuterol MDI
› Comvair MDI
› Nitrostat 0.4mg
› Hydroxyzine HCl 10mg
› Escitalopram 20mg
› Alendronate 70mg
› Isosorbide dinitrate 20mg
› Omeprazole 20mg
› Lisinopril 10mg
› Lunesta 1mg
› Promethazine 25mg
› Fluticasone nasal spray
› Loratadine
MEDICATION USE AMONG OLDER ADULTS

- Over-the-counter medication use: 46%
- Herbal and dietary supplement use: 38-49%
- Sharing medications: 13-20%

POLYPHARMACY

- Defined as either the concomitant use of multiple drugs
- or
- the administration of more medications than are indicated clinically

POLYPHARMACY BY THE NUMBERS

- Over 30% of prescription medications are taken by those over the age of 65
- Estimated 40-50% of OTC meds are consumed by older persons
- Estimated 35-50% use herbal and dietary supplements
- Approximately 15-20% share medications
- More than 80% of older people take at least one medication per day
  - Community living elders:
    - 3-4 different meds/day
  - Nursing home living elders:
    - 7-9 different meds/day
INCREASE IN PERCENTAGE OF TOTAL PRESCRIPTION UTILIZATION

Today, people age 65+ are 13% of US population, consume 33% of prescription drugs.

By 2040, people age 65+ will be 25% of population but will consume 50% of prescription drugs.

POLYPHARMACY CONCERNS

Adherence

POLYPHARMACY ADHERENCE CONCERNS:

- STRONGLY associated with ADRs
- ADEs occur in 35% of community-dwelling elderly persons
- ADEs are responsible for 5%-25% of acute hospital admissions in older adults
- In nursing homes, $1.33 is spent on ADEs for every $1.00 spent on medications
- At least 25% of all harmful ADEs in the elderly are preventable!
PREDICTORS OF ADEs

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

MOST COMMON MEDICATIONS INVOLVED IN ADVERSE DRUG EVENTS (ADEs)

- Cardiovascular drugs
- Diuretics
- NSAIDs
- Hypoglycemics
- Anticoagulants
- Medications with a narrow margin of safety

INAPPROPRIATE MEDICATIONS

- Estimated 25% of all prescribed medications for older people are potentially inappropriately selected or dosed (Beers List)
- An estimated 30% of all medications for older people are considered unnecessary
POLYPHARMACY

- Adherence Concerns
- Strongly associated with ADRs
- Increased cost
- Risk of geriatric syndromes (e.g., falls, cognitive impairment)
- Diminished functional status
- Not only associated with elderly

INAPPROPRIATE MEDICATIONS

- Estimated 25% of all prescribed medications for older people are potentially inappropriately selected or dosed (Beers List)
- An estimated 30% of all medications for older people are considered unnecessary
THE BEERS CRITERIA

- "Beers Criteria for Potentially Inappropriate Medication (PIM) Use in Older Adults"
- PIM: specific risks > benefit
- PIMs have limited effectiveness in older adults and are associated with serious problems such as delirium, GI bleeding, falls and fractures
- AHRQ website Beers Criteria
  https://www.guideline.gov/summaries/summary/49933

Link to Beers Criteria Article:
Free download from GeriatricsCareOnline.org
http://www.americangeriatrics.org/press/id:5907

BEERS CRITERIA OVERVIEW

1. PIMs and classes to avoid in older adults
2. PIMs and classes to avoid in older adults due to Drug-Disease or Drug-Syndrome Interactions That May Exacerbate the Disease or Syndrome
3. PIMs to be used with caution in older adults

An evidence based guide for clinicians and is not a substitute for professional judgment in prescribing decisions for an individual patient

BEERS CRITERIA: COMMONLY USED INAPPROPRIATE DRUGS

- Antihistamines
- Anticholinergic agents
- GI/antispasmodics
- Antipsychotics
- Benzodiazepines
- Tricyclic antidepressants
- Sedatives/hypnotics
- Anticoagulants/antiplatelets

Mark H. Beers, MD
1954-2009
### BEERS CRITERIA: COMMONLY USED INAPPROPRIATE DRUGS

Main table provides information about a drug class, the rationale for avoidance, recommendation, quality of evidence and strength of recommendation.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Rationale for avoidance</th>
<th>Recommendation</th>
<th>Quality of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td>Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as a hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity. Use of diphenhydramine such as acute treatment of allergic reactions may be appropriate.</td>
<td>Avoid</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Beers Criteria and Disease or Syndrome

<table>
<thead>
<tr>
<th>Disease or Syndrome</th>
<th>Drug(s)</th>
<th>Rationale</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>NSAIDs and COX-2 inhibitors</td>
<td></td>
<td>Avoid</td>
<td>NSAIDs: Moderate; COX-2: Moderate;</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>NON-NSAIDS, NON-COX-2 inhibitors or PPIs, or P2Y12 inhibitors</td>
<td></td>
<td></td>
<td>High Strength of Evidence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NON-NSAIDS, NON-COX-2 inhibitors or PPIs, or P2Y12 inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NON-NSAIDS, NON-COX-2 inhibitors or PPIs, or P2Y12 inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Example of Beers Criteria 2015 Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Interacting Drug Class</th>
<th>Risk Rationale</th>
<th>Recommends</th>
<th>Quality of Evidence</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines &amp; Non-benzodiazepine benzodiazepine receptor agonist hypnotics</td>
<td>2 other CNS-active drugs</td>
<td>Increased risk of falls and fractures</td>
<td>Avoid if total of ≥3 CNS-active drugs; minimize number of CNS-active drugs</td>
<td>High</td>
<td>Strong</td>
</tr>
</tbody>
</table>
GERIATRIC PHARMACOTHERAPY CHALLENGES
› More drugs are available each year
› FDA and off-label indications are expanding
› Formularies change frequently
› Prescription costs increasing
› Knowledge of medications advances
› Drugs change from prescription to OTC status
› Use of “nutraceuticals” (herbal preparations, nutritional supplements) is increasing
› Effects of aging physiology on drug therapy

CONSIDERATIONS WHEN PRESCRIBING
› Patient’s age
› Patient’s functional status
› Hepatic and Renal function
› Comorbid conditions
› Concurrent drug regimen
› Goals of care
Rational Prescribing considerations:
› Effectiveness
› Safety
› Convenience
› Cost

Pharmacodynamics ☀ and Pharmacokinetics ☀

What the body does to the drug
What the drug does to the body
PHARMACODYNAMICS & AGING

- Changes with aging:
  - Alterations in receptor number
  - Alterations in drug receptor affinity
  - Enhanced or diminished response

Physiologic Changes with Aging

PHARMACOKINETICS (PK)

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance and gait</td>
<td>•↓ Stride length and slower gait</td>
</tr>
<tr>
<td></td>
<td>•↓ Arms swinging</td>
</tr>
<tr>
<td></td>
<td>•↑ Body sway when standing</td>
</tr>
<tr>
<td>Body composition</td>
<td>•↓ Total body water</td>
</tr>
<tr>
<td></td>
<td>•↓ Body fat</td>
</tr>
<tr>
<td></td>
<td>•↑ Serum albumin</td>
</tr>
<tr>
<td></td>
<td>•↑ or ↓ Albumin glycoprotein (α1-Acid glycoprotein) (* or ↑ by several disease states)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>•↓ Cardiac output</td>
</tr>
<tr>
<td></td>
<td>•↑ Systemic vascular resistance with loss of arterial elasticity and dysfunction of systems maintaining vascular tone</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>•↓ Number of receptors of all types and ↑ sensitivity of remaining receptors</td>
</tr>
<tr>
<td></td>
<td>•↓ Short-term memory, coding and retrieval, and executive function</td>
</tr>
<tr>
<td></td>
<td>•↑ Altered sleep patterns</td>
</tr>
<tr>
<td>Endocrine</td>
<td>•↓ Estrogen, testosterone, TSH, and DHEA-S levels</td>
</tr>
<tr>
<td></td>
<td>•↑ Altered insulin signaling</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>•↓ Motility of the large intestine</td>
</tr>
<tr>
<td></td>
<td>•↓ Vitamin absorption by active transport mechanisms</td>
</tr>
<tr>
<td></td>
<td>•↓ Splanchnic blood flow</td>
</tr>
<tr>
<td></td>
<td>•↓ Bowel surface area</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>•↓ Atrophy of the vagina with decreased estrogen</td>
</tr>
<tr>
<td></td>
<td>•↓ Reduced hypothalamic-pituitary-hormone changes</td>
</tr>
<tr>
<td></td>
<td>•↓ Detrimental hypothalamic-pituitary-hormone changes</td>
</tr>
<tr>
<td></td>
<td>•↓ Detrimental hypothalamic-pituitary-hormone changes</td>
</tr>
<tr>
<td>Hepatic</td>
<td>•↓ Hepatic size</td>
</tr>
<tr>
<td></td>
<td>•↓ Reduced blood flow</td>
</tr>
<tr>
<td></td>
<td>•↓ Poised platelets, neutrophiles, lymphocytes</td>
</tr>
</tbody>
</table>
Physiologic Changes with Aging

Organ System | Manifestations
--- | ---
Immune | •↓ Antibody production in response to antigens
•↑ Autoimmunity
Oral | •↓ Abnormal dentition
•↑ Ability to taste salt, bitter, sweet, and sour
Pulmonary | •↓ Respiratory muscle strength
•↓ Inter-alveolar interdependence
•↓ Arterio-arterial shunt
•↓ Arterial oxygenation and impaired carbon dioxide elimination
•↓ Maximum breathing capacity
•↓ Residual volume
Renal | •↓ GFR
•↓ Renal blood flow
•↓ Filtration fraction
•↓ Tubular secretory function
•↓ Renal mass
•↓ Vital capacity
•↓ Maximal breathing capacity
•↑ Residual volume

Sensory | •Presbyopia (diminished ability to focus on near objects)
•↓ Night vision
•Presbycusis (high-pitch, high-frequency hearing loss)
•↓ Sensation of smell and taste
Skeletal | •↓ Skeletal bone mass (osteopenia)
•↓ Joint stiffening caused by reduced water content in tendons, ligaments, and cartilage
Skin/hair | •Thinning of stratum corneum
•↓ Langerhans cells, melanocytes, and mast cells
•↓ Depth and extent of the subcutaneous fat layer
•Thinning and graying of hair caused by more hairs in the resting phase and shortening of the growth phase as well as changes in follicular melanocytes

**Pharmacokinetic Parameters**

**Gastrointestinal absorption**
- Unchanged passive diffusion and no change in bioavailability for most drugs
- Active transport and ↓ bioavailability for some drugs
- First-pass metabolism; ↓ bioavailability for some drugs, and ↓ bioavailability for some prodrugs

**Distribution**
- Volume of distribution and ↑ plasma concentration of water-soluble drugs
- Increase in distribution and ↑ terminal disposition half-life (t1/2) for lipid-soluble drugs

**Hepatic metabolism**
- Clearance and ↓ t1/2 for drugs with poor hepatic extraction (capacity-limited metabolism); phase I metabolism may be affected more than phase II
- Clearance and ↓ t1/2 for drugs with high hepatic extraction ratios (flow-limited metabolism)

**Renal excretion**
- Clearance and ↓ t1/2 for renally eliminated drugs and active metabolites
HEPATIC METABOLIC PATHWAYS MATTER
MAKING COMPOUND MORE POLAR AND WATER SOLUBLE

- **Phase I pathways** (e.g., oxidation, reduction, and hydrolysis) convert drugs to metabolites with <, =, or > pharmacologic effect than parent compound
  - MOST affected with age
  - CYP450: 1A2, 2A6, 2B6, 2C8/9, 2C19, 2D6, 2E1. CYP3A4 is involved in more than 50% of drugs on the market
  - Source of drug-drug interactions

- **Phase II pathways** conjugate drugs to inactive metabolites that do not accumulate
  - LESS affected with age
  - With few exceptions, drugs metabolized by phase II pathways are preferred for older patients

KEY CONCEPTS FOR DRUG ELIMINATION

- **Half-life**: time for serum concentration of drug to decline by 50%
  - Majority of medications
  - Exceptions include phenytoin

- **Clearance**: volume of serum from which the drug is removed per unit of time—L/hour or mL/minute

CREATININE CLEARANCE (CrCl)

- Used to make dosing adjustments in patients with renal dysfunction
  - ↓ lean body mass → lower creatinine production
  - ↓ glomerular filtration rate (GFR)

Result: In older persons, Scr does NOT reflect CrCl
PHARMACODYNAMIC CHANGES OF AGING

Central nervous system sensitivity
- Enhanced receptor response
- Reduced CNS dopamine
- Increased EPS symptoms
- Reduced serotonin receptor function
- Enhanced sensitivity to antidepressants
- Altered GABA-benzodiazepine receptor function
- Increased sensitivity to benzodiazepine, alcohol, barbiturate
- Reduced CNS acetylcholine
- Enhanced anticholinergic side effects
- Sedation, confusion, psychosis, delirium
- Urinary retention, constipation
- Decline in various measures of cognitive function, especially in the very old or those with preexisting dementia

Medication Appropriateness Index

Questions to Ask About Each Individual Medication
1. Is there an indication for the medication?
2. Is the medication effective for the condition?
3. Is the dosage correct?
4. Are the directions correct?
5. Are the directions practical?
6. Are there clinically significant drug–drug interactions?
7. Are there clinically significant drug–disease or drug–condition interactions?
8. Is there unnecessary duplication with other medication(s)?
9. Is the duration of therapy acceptable?
10. Is this medication the least expensive alternative compared with others of equal utility?

COMMONLY OVERPRESCRIBED AND INAPPROPRIATELY USED DRUGS

- Anti-infective agents
- Anticholinergic agents
- Urinary & GI antispasmodics
- Antipsychotics
- Benzodiazepines
- Digoxin for diastolic dysfunction
- Dipyridamole
- H$_2$ receptor antagonists
- Laxatives & fecal softeners
- NSAIDs
- Proton-pump inhibitors
- Sedating antihistamines
- Tricyclic antidepressants
- Vitamins and minerals

STOPP
**COMMONLY UNDERPRESCRIBED DRUGS**
- ACE inhibitors for patients with diabetes and proteinuria
- Angiotensin-receptor blockers
- Anticoagulants
- Angiotensin II (AT1) receptor blockers
- Beta-blockers for patients after MI or with heart failure
- Diuretics for uncontrolled hypertension
- Bronchodilators
- Proton-pump inhibitors or misoprostol for GI protection from NSAIDs
- Statins
- Vitamin D and calcium for patients with or at risk of osteoporosis
- **START**

  “Start low and go slow, but GO!”

**DUPLICATE MEDICATIONS**

- Duplicate medications may contain the same active ingredient
  - Vicodin and Tylenol PM
- More than one drug from the same general pharmacologic class
  - Aleve and ibuprofen

**PREScribing CASCADE and importance of “First Think Drugs”**

**Drug 1** - Metoclopramide →
- EPS ADE misinterpreted as a new medical condition → Parkinsonism with Rx to treat EPS ADE

**Drug 2** - CCB + Treatment of Parkinsonism →
- Peripheral edema ADE misinterpreted as a new medical condition → Diuretic Rx to treat ADE → electrolyte disorder of hypokalemia
  - Hypokalemia ADE misinterpreted as a new medical condition
  - Potassium supplement → GI distress → antacid → constipation
**DRUG-DRUG INTERACTIONS**

- Consequences
  - Decreased efficacy
  - Unexpected side effects
  - Increase the activity of a drug
- May lead to ADEs
  - Confusion/delirium, cognitive impairment, hypotension, acute renal failure
- Likelihood ↑ as number of medications ↑

**COMMON DRUG-DISEASE INTERACTIONS**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk or fall of falls</td>
<td>Benzodiazepines</td>
<td>Falls/fractures</td>
</tr>
<tr>
<td>Dementia</td>
<td>TCA, Antipsychotics</td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>NSAIDs</td>
<td>AKI</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>ASA, NSAIDs</td>
<td>GI bleeding</td>
</tr>
<tr>
<td>CHF</td>
<td>Non-hydroxytamidine, CCB</td>
<td>Pulmonary edema, worsening l/s</td>
</tr>
<tr>
<td>BPH</td>
<td>TCA</td>
<td>Urinary frequency</td>
</tr>
<tr>
<td>Constipation</td>
<td>Opioids</td>
<td>Worsening constipation</td>
</tr>
</tbody>
</table>

**COMMON FOOD INTERACTIONS**

- Dairy products
- Coffee/Tea
- Grapefruit Juice
- Alcohols
- Charcoal-Broiled foods
- Green leafy vegetables
- Licorice
- Ginseng
Our Case: 78 year old female

- First visit
  - Medications 21 (originally 36: duplicates, discontinued)
  - Likely Problems 12
  - Medical providers 6

Doing the math--
- 2 problems for each provider prescribing 6 different medications

Medication List Rearranged in EHR

- Carvedilol 3.125mg
- Isosorbide dinitrate 20mg
- Lisinopril 10mg
- Aspirin 81mg
- Atorvastatin 40mg
- Nitroglycerin 0.4mg
- Fluticasone & Salmeterol HFA 230-21
  - Fluticasone nasal spray
  - Albuterol MDI
  - Ipratropium & albuterol
  - Loratadine

- Cimetidine 400mg
- Omeprazole 20mg
- Promethazine 25mg
- Morphine ER 15mg
- Morphine ER 30mg
- Morphine IR 15mg
- Aklidronate 70mg
- Escitalopram 20mg
- Eszopiclone 1mg
- Hydroxyzine HCl 10mg

SUMMARY

- Rational 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

- A 69-year-old woman comes to the office to establish care. She reports that she often feels sleepy.
- History includes osteoporosis, hip fracture, systolic heart failure, hypertension, frequent falls, chronic kidney disease, and post-herpetic neuralgia.
- Medications include metoprolol XL 100mg PO daily, gabapentin 600mg PO TID, alendronate 35mg PO weekly, vitamin D 800 IU PO daily, calcium carbonate 500mg PO TID with meals, and aspirin 81mg PO daily.
- Serum creatinine is 1.5 mg/dL, with estimated creatinine clearance of 30 mL/min.

Which of the following would be most likely to relieve this patient’s sleepiness?

A) Reduce gabapentin dosage to 600mg PO BID
B) Start modafinil 200mg PO daily
C) Discontinue alendronate
D) Increase vitamin D to 1200 IU PO daily
E) Switch metoprolol XL to immediate-release metoprolol 50mg PO BID

CASE 2

- A 75-year-old man comes for a follow-up office visit 2 weeks after hospital discharge. He had been admitted for exacerbation of heart failure.
- He has atrial fibrillation, hypertension, systolic heart failure (NYHA class III), and coronary artery disease.
- Medications include furosemide 20mg PO Q12H, potassium 10mEq PO daily, lisinopril 10mg PO daily, warfarin 2mg PO daily, metoprolol 25mg Q12H, and, since hospital discharge, spironolactone 12.5mg PO daily.
- On examination, the patient’s weight is stable and he has returned to baseline function.
CASE 2

• Laboratory tests:

<table>
<thead>
<tr>
<th>Test</th>
<th>At discharge</th>
<th>Today</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>137</td>
<td>139</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.7</td>
<td>5.3</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Which of the following is the most appropriate next step?

A) Discontinue spironolactone  
B) Discontinue potassium supplement  
C) Decrease lisinopril dosage  
D) Increase lisinopril dosage  
E) Change furosemide schedule to a single daily dose

References

- Agency for Healthcare Research and Quality web site Beers Criteria
  https://www.guideline.gov/summaries/summary/49933
- STOPP/START criteria for potentially inappropriate prescribing in older people: version 2 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4339726/
- Lexi-Comp app
- Epocrates app