America’s other drug problem: How to avoid medication-related problems in older adults

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Learning Objectives

At the conclusion of the lecture the pharmacist learner shall be able to:
• Describe the effects of aging on pharmacokinetic parameters (absorption, distribution, metabolism, and elimination).
• Describe the effects of aging on pharmacodynamic parameters.
• Discuss basic principles of prescribing for older patients to avoid adverse drug effects.
• Identify potentially inappropriate medications in a given geriatric patient based on the 2015 Beers’ criteria and potential alternative treatment options.

Learning Objectives

At the conclusion of the lecture the pharmacy technician learner shall be able to:
• List 3 physiologic changes in older adults that increase the risk of drug side effects.
• List 3 basic principles of prescribing medications for older adults.
• List 3 common medications on the 2015 Beers’ criteria that are potentially inappropriate in an older adult.

Why are geriatric pharmacokinetics important?

• Persons aged 65 and older are prescribed the highest proportion of medications in relation to their percentage of the U.S. population
  • Now, 13% of total population buy 33% of all prescription drugs
  • By 2040, 25% of total population will buy 50% of all prescription drugs

Adverse drug events in older adults

• ADEs are responsible for 5% to 28% of acute geriatric hospital admissions
• ADEs occur in 35% of community-dwelling elderly persons
• ADEs incidence: 26/1000 hospital beds
• In nursing homes, $1.33 spent on ADEs for every $1.00 spent on medications

Which of the following principles should NOT be followed when prescribing new medication(s) for a geriatric patient?

A. Start with a low dose
B. Start all new medications simultaneously
C. Titrates the dosage upward slowly
D. Use one drug to treat two different conditions, if possible
Risk of adverse drug events in older adults

- Increased risk of adverse drug events
  - Multiple medications
    - >20% of elderly use 5 or more medications
    - Increased frequency of drug-drug interactions
    - Decreased medication adherence
  - Multiple comorbidities
  - Age-related changes in drug pharmacokinetics
  - Age-related changes in drug pharmacodynamics

RISK FACTORS FOR ADEs

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

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

ADE PRESCRIBING CASCADE

- Adverse drug effect - misinterpreted as a new medical condition

Before Starting a New Medication, Ask:

- 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?

PHARMACOKINETICS

- Absorption
- Distribution
- Metabolism
- Elimination
Aging and Absorption

- Clinical significance is not well characterized
  - Most drugs absorbed through passive diffusion in the proximal small bowel
- Exception: levodopa
  - Threefold increase in bioavailability due to reduced activity of dopamine decarboxylase in the stomach wall

Absorption

- Alterations in GI function
  - Decreased gastric parietal cell function
    - Decrease in secretion of hydrochloric acid
    - Increase in gastric pH
  - Decreased rate of gastric emptying
    - Anticholinergics, opiates, Fe, anticonvulsants
  - Drug-drug interactions
    - Divalent cations (calcium, magnesium, iron) and fluoroquinolones (e.g., ciprofloxacin)

Absorption

- Topical absorption (patches, creams, ointments, etc.)
  - Thinning and reduction of absorptive surface
    - Skin atrophy and decreased fat content
      - Reduction in vascular network and risk of contact dermatitis

Effects of aging on volume of distribution (Vd)

- Depends mostly on physiochemical properties of individual medications
  \[
  t_{1/2} = \frac{0.693 \times V_d}{C_l}
  \]

Physiologic Changes in Older Adults that impact Vd

- ↓ body water (10-15%) → lower Vd for hydrophilic drugs
  - Warfarin, digoxin, lithium, cimetidine, APAP, ETOH
- ↓ lean body mass → lower Vd for drugs that bind to muscle
- ↑ fat stores → higher Vd for lipophilic drugs
  - Diazepam, lidocaine, TCAs, propranolol

Distribution:

- Decreased serum albumin
  - 10% to 20% in hospitalized or poorly nourished patient
  - Increase in unbound fraction of highly protein bound acidic drugs
    - Monitor drug levels—free phenytoin level with low albumin
  - Warfarin, phenytoin, naproxen
- Increased α-1 acid glycoprotein
  - Decrease in unbound fraction of highly protein bound basic drugs
    - Lidocaine, propranolol, imipramine

Distribution:

- Protein Binding
Aging and Metabolism

- The liver is the most common site of drug metabolism
- Decrease in liver blood flow
  - 40% to 45% with aging, related to cardiac function
  - Increase in bioavailability
  - Decreased 1st pass effect = more parent drug
- Decrease in liver size
  - 20% to 50% decrease in absolute weight up to age 80
  - Reduction of total amount of metabolizing enzymes
  - Leads to decrease in CI and increase in t½
  - Start with lower dosage
  - Caution with toxic metabolites
    - Meperidine

Based on the above table, which of the following statements most likely explains the change in volume of distribution for DRUG ABC (a lipophilic drug, >90% protein binding to α-1 acid glycoprotein) with increasing age?

A. An increase in the percentage of lean body mass with age
B. An increase in the unbound fraction of highly protein bound basic drugs
C. A decrease in the unbound fraction of highly protein bound acidic drugs
D. An increase in the percentage of fat body mass with age

The Effects of Aging on the Kidney

- Kidney size
- Renal blood flow
  - ~1%/year after age 50
- Number of functioning nephrons
- Renal tubular secretion
- Result: Lower glomerular filtration rate
  - ~35% in healthy individuals between ages 20 and 90
  - Accumulation increases risk of toxicity
    - Lithium, aminoglycosides, captopril, NSAIDs

Serum Creatinine does NOT reflect Creatinine Clearance

- Lower lean body mass → lower creatinine production and
  - Lower glomerular filtration rate (GFR)

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

How to Calculate Creatinine Clearance

- Measure:
  - Time-consuming to be accurate
  - Requires 24-h urine collection
  - 8-h collection may be accurate but not widely accepted
- Estimate:
  - Cockroft and Gault equation
  - MDRD
Cockroft and Gault Equation

\[
\text{Ideal weight in kg} \times \frac{140 - \text{age}}{72} \times (0.85 \text{ if female})
\]

An elderly person with a serum creatinine in the normal range may actually have a decreased creatinine clearance because they have:

A. Increased creatinine production and an increased glomerular filtration rate (GFR)
B. Increased creatinine production and a decreased GFR
C. Decreased creatinine production and a decreased GFR
D. Decreased creatinine production and an increased GFR

Pharmacodynamics

Definition
- Time course and intensity of pharmacologic effect of a drug
- Impairment varies considerably from person to person
- All organ systems are affected
- Kidneys, liver, GI, CNS, CV, GU

Altered Pharmacodynamic Mechanisms

- Change in receptor numbers
- Change in receptor affinity
- Postreceptor alterations
- Age-related impairment of homeostatic mechanisms

CNS

- Changes are significant, yet idiosyncratic
  - Decrease in weight and volume of brain
  - Alterations in cognition
- Increased sensitivity to medications
  - Benzodiazepines, opioids, anticholinergics, NSAIDs

CNS

- Cholinergic blockade
  - Sedation, confusion, and reduced ability to recall
    - TCAs, diphenhydramine, antispasmodics, antipsychotics
- Benzodiazepines can cause severe CNS depression
  - Leads to falls and hip fractures
  - Use caution and small dosages
Cardiovascular

- Decreased baroreceptor responsiveness
  - Results in orthostatic hypotension
    - Antihypertensives

GU

- Urinary incontinence
  - 15 to 30% of community-dwellers
  - 50% of nursing home residents
  - Enlarged prostate, urine retention

Inappropriate Medication Use in Older Adults (2015 Beers Criteria update)

- Medications or classes to avoid in older adults
- Diseases/conditions and medications to avoid in older adults with these diseases

Beers’ Criteria: Independent of Diagnosis

Analgesics

- Meperidine (long t1/2 metabolite, CNS)-Avoid
- Non-COX-selective NSAIDs, oral
  - Indomethacin (CNS)-Avoid
  - Ketorolac–(GI bleeds)-Avoid
- Avoid chronic use of all others unless alternatives are not effective and patient can take gastroprotective agent
  - Aspirin >325 mg/day
- Skeletal muscle relaxants*
  - (? Effectiveness/anticholinergic SE)-Avoid

Psychiatric/CNS

- Antidepressants
  - Amitriptyline, doxepin >6 mg/day, clomipramine, nortriptyline, paroxetine, trimipramine (anticholinergic, orthostasis)
- Hypnotics/Anxiolytics
  - Benzodiazepines (CNS/FAILS)
    - Short, intermediate, and long-acting
    - Long-acting may be appropriate for seizures/REM sleep*
  - Nonbenzodiazepine hypnotics
    - Zopiclone, zolpidem, zaleplon (CNS, falls, min. improvement sleep latency/duration)
- Antipsychotics
  - All 1st and 2nd generation antipsychotics-Avoid
  - Except in schizophrenia, bipolar, and short-term use with chemotherapy*

Cardiovascular

- Alpha blockers (orthostasis)
  - Doxazosin, prazosin, terazosin
- Alpha agonists, central (orthostasis)
  - Clonidine, methyldopa, guanabenz, guanfacine
- Amiodarone
  - Avoid 1st-line a. fib unless has heart failure
- Dronedarone
  - Avoid permanent a. fib/severe heart failure
- Digoxin- avoid 1st-line a. fib/heart failure
Beers’ Criteria: Independent of Diagnosis
Endocrine and GI
• Sulfonylureas, long-duration (hypoglycemia/SIADH)
  o Chlorpropamide and glyburide
• Insulin, sliding scale
• Megestrol
• Growth hormone
• Estrogen (oral and topical patch)
• Androgens: testosterone
• Desiccated thyroid (cardiac effects)
• Metoclopramide (EPS)
• Mineral oil, oral (aspiration)
• Proton pump inhibitors [C. difficile/bone loss/bone fractures]
  o Avoid use >8 weeks, unless high-risk patients

Beers’ Criteria: Independent of Diagnosis
anticholinergics and anti-infective
• Antihistamines (anticholinergic)
  o Diphenhydramine, oral (confusion/sedation)
  o Chlorpheniramine
  o Meclazine
  o Promethazine
  o Hydroxyzine
• Antiparkinson agents
  o Benztropine, trihexyphenidyl
• Antispasmodics-Avoid, except palliative care
  o Belladonna, dicyclomine, hyoscyamine, scopolamine
• Nitrofurantoin
  o Avoid long-term suppression and CrCl<30 mL/min

Beers Criteria
Considering Diagnosis
• Heart failure: NSAIDs/COX-2 inhibitors, TZDs
  o diltiazem/verapamil (avoid reduced EF)
• Syncope: AChEIs, alpha blockers, tertiary TCAs
• Chronic seizures: bupropion, tramadol, olanzapine
• Delirium: TCAs, anticholinergics, benzos, H2RA, sedative hypnotics
• Dementia: anticholinergics, benzos, antipsychotics, H2RA
• Falls/Fractures: Anticonvulsants, antipsych, benzos, nonbenzo hypnotics, opiatel TCAs, SSRIs
• Insomnia-decongestants, theophylline, methylphenidate, modafinil [CNS stimulants]
• Parkinson disease:
  o All antipsychotics (except quetiapine/clozapine)
  o Antipsychotics: metoclopramide, prochlorperazine, promethazine

Beers Criteria
Considering Diagnosis
• Gastric/duodenal ulcers-NSAIDs and aspirin >325 mg
• CKD (stage IV/V): NSAIDs
• Urinary incontinence in women
  o All types: estrogen (oral and transdermal)
  o Stress/mixed: alpha blockers
• BPH: strong oral anticholinergics (except for UI)

To be used with caution
• Aspirin for primary prevention, age ≥ 80 years
• Dabigatran, age ≥75 years and CrCl<30 mL/min
• May cause SIADH/hyponatremia
  o Antipsychotics
  o Diuretics
  o SSRIs
  o SNRIs
  o TCAs
  o Mirtazapine

Potentially Important Drug-Drug Interactions
• Multiple anticholinergics
• Increased risk of falls:
  o Benzodiazepines
  o Antidepressants (SSRIs/TCA)
  o Antipsychotics
  o Opioids
• Corticosteroids/NSAIDs
• Peripheral alpha-blockers/loop diuretics
  o Increase risk urinary incontinence in older women
• Warfarin/NSAIDs
To be avoided or have their dosage reduced with varying levels of kidney function

- Refer to table 6 for full list
- Examples:
  - Colchicine (CrCl <30) reduce dose
  - Gabapentin (CrCl <60) reduce dose
  - Enoxaparin (CrCl <30) reduce dose
  - Rivaroxaban (CrCl 30-50) reduce dose
  - Spironolactone (CrCl <30) Avoid
  - Triamterene (CrCl <30) Avoid

Inappropriate Drug Therapy based on Beers' Criteria

<table>
<thead>
<tr>
<th>Authors</th>
<th>Setting</th>
<th>Prevalence of Inappropriate Prescribing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goulding MR 2004</td>
<td>Ambulatory care visits</td>
<td>7.8% of visits</td>
</tr>
<tr>
<td>Zhan et al. 2001</td>
<td>Community dwelling elderly</td>
<td>21.3% of patients</td>
</tr>
<tr>
<td>Simon SR, et al. 2005</td>
<td>Elderly in managed care</td>
<td>28.8% of patients</td>
</tr>
<tr>
<td>Golden et al. 1999</td>
<td>Nursing home-eligible</td>
<td>39.7% of patients</td>
</tr>
<tr>
<td>NM Medicare Advantage plans 2009</td>
<td>New Mexico Medicare patients</td>
<td>21.5% of patients</td>
</tr>
</tbody>
</table>

Alternatives to Beers criteria

- 2015 new alternatives published
  - Refer to American Geriatric Society

STOPP and START Criteria

- Screening Tool of Older Persons’ Prescriptions (STOPP)
- Screening Tool to Alert doctors to Right Treatment (START)

Conclusions

- Age alters pharmacokinetics (drug absorption, distribution, metabolism, and elimination)
- Age alters pharmacodynamics
- ADEs are common among older patients
- Successful drug therapy means:
  - Choosing the correct dosage of the correct drug for the condition and individual patient
  - Monitoring the therapy

References/Additional Reading

## Case: AB 81 year-old female

### Problem List

1. CVA × 6
2. Carotid stenosis
3. Right endarterectomy in 6/05
4. Osteoarthritis
5. Chronic constipation
6. Diabetes
7. Peripheral neuropathy
8. Coronary artery disease
9. Hypertension
10. Hyperthyroidism
11. Hypercholesterolemia
12. Osteopenia
13. Urinary incontinence
14. Recurrent pyelonephritis
15. Atrophic vaginitis
16. Reactive airway disease

### AB’s Medications

1. Levothyroxine 75 mcg daily
2. Lovastatin 10 mg, 2 tablets at bedtime
3. Clopidogrel 75 mg daily
4. Nitroglycerin SL tabs 0.4 mg prn
5. Amlodipine 10 mg daily
6. Furosemide 20 mg daily
7. Potassium 10 mEq, 2 tablets twice daily
8. Clonidine 0.2 mg, 2 tablets twice daily
9. Metoprolol 50 mg twice daily
10. Novolin 70/30, 25 units qam, 15 units qpm

### Case AB Objective:

- **Vital Signs:**
  - BP 168/63
  - HR 79
  - RR 24
  - Temp. 97.8°F
  - Weight 177.9 lbs.
  - Pain 1/10

- **Lab Values:**
  - Na 140
  - K 4.8
  - Cl 104
  - BUN 25
  - Scr 1.3

- **HbA1c 6.8%**
- **Mean blood glucose 164.8**
- **TSH 5.680**
- **Lipids**
  - TC 144
  - TG 258
  - HDL 39
  - LDL 53

### AB’s Medications (continued)

19. Docusate 100 mg bid
20. Mineral oil pm constipation
21. Glycerin suppositories pm constipation (uses about 2x/week)
22. Aspirin 81 mg daily
23. Diphenhydramine 25 mg at bedtime for sleep (uses 3-4 x/week)
24. Calcium 500 mg with vitamin D bid
25. Glucosamine 2 caps qd