Geriatric Pharmacotherapy

Stephen Rupp, RPh, BCPS
University Hospital O.R. Pharmacy Services
Objectives

1. Understand the effect of aging on Pharmacokinetics and Pharmacodynamics.
2. Increase awareness of medications inappropriate in the elderly.
3. Application of Beer’s/ Agency for healthcare Research and Quality (AHRQ) criteria to determine extent of inappropriate prescribing (VA Study 2000)
4. Discuss top 10 Dangerous Drug Interactions in Long-Term care
5. Understand/ apply principles of drug prescribing in the elderly.
Medications & The Elderly is it a Problem?

• 10.7% of hospital admissions in older adults are associated with adverse drug reactions.
• Older adults are seven times more likely to be hospitalized for an adverse event than younger individuals. Warfarin, insulin and digoxin together account for over one-third of ER department visits for adverse drug events among older adults.
• About 1 in 3 older persons taking at least 5 medications will experience an ADR event each year. 25% of older adults takes 5 or more medications on a regular basis.
Challenges of Geriatric Pharmacotherapy?

- New medications on market.
- Increase usage off-label.
- Managed care formularies.
- Increase usage of “nutraceuticals”.
- Multiple co-morbid states.
- Polypharmacy
- Increased understanding of drug –drug interactions.
- Effects of aging on drug therapy (pharmacokinetics/pharmacodynamics)
- Compliance
- Drug cost
Pharmacokinetics (PK)

- LADME
- Liberation - the process of release of drug from the formulation.
- Absorption - the process of a substance entering the blood circulation.
- Distribution - the dispersion or dissemination of substances throughout the fluids and tissues of the body.
- Metabolism - the irreversible transformation of parent compounds into daughter metabolites.
- Excretion - the elimination of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.
Aging and Absorption

- Gastrointestinal System
  - Splanchnic blood flow decreased – which can decrease rate of absorption and delay time to peak concentration. Overall amount absorbed bioavailability is UNCHANGED.
- RARELY CLINICALLY SIGNIFICANT
Aging and Drug Distribution

- Distribution: effect of the concentration available at the target
- Hydrophilic vs. Lipophilic
- Protein Binding
- \( C = \frac{D}{V_d} \)
  - \( C \) = concentration
  - \( D \) = dosage
  - \( V_d \) = Volume of distribution
<table>
<thead>
<tr>
<th>Aging Effect</th>
<th>VD Effect</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Body Water</td>
<td>↓ Hydrophilic Drugs</td>
<td>Ethanol, Lithium</td>
</tr>
<tr>
<td>↓ Lean Body Mass</td>
<td>↓ Drugs that bind to muscle</td>
<td>Digoxin</td>
</tr>
<tr>
<td>↑ Fat Stores</td>
<td>↑ Lipophilic Drugs</td>
<td>Diazepam, Trazadone</td>
</tr>
<tr>
<td>↓ Albumin</td>
<td>↑ Unbound drug (↑ free / active drug)</td>
<td>Diazepam, Valproic Acid, Phenytoin, Warfarin</td>
</tr>
<tr>
<td>↑ α1 Acid Glycoprotein</td>
<td>↓ Unbound drug (↓ free/active drug)</td>
<td>Quinidine, Propranolol, Amitriptylline, Erythromycin</td>
</tr>
</tbody>
</table>
Aging and Metabolism

Drug (Lipid-soluble, Nonpolar)

Phase 1

Biotransformation
- Oxidation
- Hydrolysis
- Reduction

Metabolite A

Phase 2

Synthesis
- Conjugation with Glycine
- Sulfate
- Glucuronic Acid

Metabolite C

Metabolite B

(Metabolite: Water-soluble, Polar)

Excretion (Urine and Bile)
<table>
<thead>
<tr>
<th>PATHWAY</th>
<th>EFFECT</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Metabolites are equal, lesser or greater</td>
<td>Diazepam, quinidine, piroxicam, theophylline</td>
</tr>
<tr>
<td>Phase II</td>
<td>Conversion to inactive metabolites</td>
<td>Lorazepam, oxazepam, temazepam</td>
</tr>
</tbody>
</table>

Medications undergoing phase II hepatic metabolism are generally preferred in the elderly due to inactive metabolites, thus reducing the accumulation of a medication.
Aging Effects on Hepatic Metabolism

- Metabolic clearance of drugs by the liver may be reduced
  - Due to decreased hepatic blood flow
  - Decreased liver size and mass

- Phase I metabolic processes are decreased in aging. If a large first pass then increased bioavailability

- Phase II metabolic processes are generally preserved
Drug Elimination Concepts

- **Half-Life**
  Time for serum concentration of the drug to decline by 50% (expressed in hours)

- **Clearance**
  Volume of serum from which the drug is removed per unit of time (expressed in ml/min)

\[\downarrow \text{Elimination} \rightarrow \uparrow \text{drug accumulation} \rightarrow \uparrow \text{Toxicity}\]
Effects of Aging on the Kidney

- Decreased kidney size
- Decreased renal blood flow
- Decreased number of functioning nephrons
- Decreased tubular secretion

RESULT IS A DECREASE IN GLOMERULAR FILTRATION RATE.

GFR is estimated using Creatinine Clearance. Creatinine is also reduced in aging.
**Effects of Aging on the Kidney**

Estimating Creatinine Clearance Cockroft Gault

\[(IBW \text{ in Kg}) \times 140 \text{-age} \times 0.85 \text{ for females}
\]

\[72 \times (SCr \text{ in mg/dl})\]

**Example 5’5”- 55 kg female**

<table>
<thead>
<tr>
<th>AGE</th>
<th>SCr</th>
<th>CrCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1.1</td>
<td>65</td>
</tr>
<tr>
<td>50</td>
<td>1.1</td>
<td>53</td>
</tr>
<tr>
<td>70</td>
<td>1.1</td>
<td>41</td>
</tr>
<tr>
<td>90</td>
<td>1.1</td>
<td>30</td>
</tr>
</tbody>
</table>
Pharmacodynamics

• The study of the interaction of the pharmacologic agent and its target tissue: measuring the intensity, peak, duration and determining the mechanism of physiological action.

Examples:

↑ Level and duration of pain relief with opiates
↓ HR response to beta blockers
↑ Sensitivity to sedation and psychomotor impairment with benzodiazepines
↑ Cardiac sensitivity to Digoxin
PK & PD Summary

• PK and PD changes generally result in decreased clearance and increased sensitivity to medications in the elderly
• Use of lower doses, longer intervals and slower titration are helpful in decreasing adverse drug events in the elderly
• Practical knowledge of medications known to cause ADE’s as well as drug–drug interactions is prudent and necessary to prescribe with confidence in the elderly.
Drug Interactions

• Too many to list all.
• 2 medications=13% risk ADR
• 5 medications=38% risk ADR
• >7 medications=82% risk ADR
• Preventable drug interactions account for about ½ of all ADR’S.

Medication Management Project
Top 10 Drug Interaction List

- **Challenge:** Sort through the hundreds of DI’s to find the most relevant in clinical significance.
- **Nominations were solicited from listserver group of 500 geriatric clinicians**
- **Survey instrument prepared and distributed then compiled at the AMDA and ASCP meetings (2001).**

  - [www.scoup.net](http://www.scoup.net) M# Project
### Top 10 Drug Interactions In Long Term Care

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Impact</th>
<th>Mechanism of Interaction</th>
<th>Prevent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warf/ NSAID</td>
<td>Gi BLEED</td>
<td>GI Irritate/ Platelet Effect</td>
<td>APAP COX -2 Inhib</td>
</tr>
<tr>
<td>Warf/ Sulfa</td>
<td>Inc. Bleeding-</td>
<td>Decrease K-Anti B</td>
<td>Other Anti B reduce warf 50%</td>
</tr>
<tr>
<td>Warf / Macrolide</td>
<td>Inc Bleeding</td>
<td>Decrease K – Anti B</td>
<td>Other Anti B</td>
</tr>
<tr>
<td>Warf/ Quinolone</td>
<td>Inc Bleeding</td>
<td>Decrease K – Anti B</td>
<td>Other Anti B</td>
</tr>
<tr>
<td>Warf / DPH</td>
<td>Variable Warf/ DPH</td>
<td>?</td>
<td>Monitor INR/ DPH</td>
</tr>
<tr>
<td>Interaction</td>
<td>Impact</td>
<td>Mechanism of Interaction</td>
<td>Prevent</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------------</td>
<td>--------------------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>ACE Inhib/ K + Supp</td>
<td>Inc Serum K+</td>
<td>Decrease Alldosterone Production</td>
<td>Know K+ Level</td>
</tr>
<tr>
<td>ACE Inhib/ Spironolactone</td>
<td>Inc Serum K+</td>
<td>Additive Effect?</td>
<td>Know K+ Level</td>
</tr>
<tr>
<td>Digoxin / Amiodarone</td>
<td>DIG Toxicity</td>
<td>Decrease DIG clearance</td>
<td>DIG level, decrease dose 50%/ Monitor</td>
</tr>
<tr>
<td>Digoxin / Verapamil</td>
<td>DIG Toxicity</td>
<td>Synergistic Slow Impulse</td>
<td>Use DIG CHF?</td>
</tr>
<tr>
<td>Theophylline/ Quinolones</td>
<td>Theophylline Toxicity</td>
<td>Inhibition Hepatic Metab Theo</td>
<td>Theo level- Use Levo- Moxi less DI</td>
</tr>
</tbody>
</table>
Beers Criteria

- The Beers Criteria (or Beers List) is a list of medications that are generally considered inappropriate when given to elderly people. For a wide variety of individual reasons, the medications listed tend to cause side effects in the elderly due to the physiologic changes of aging. The list was originally created by geriatrician Mark H. Beers.¹
## Beers List: High Potential for Severe Adverse Outcome

<table>
<thead>
<tr>
<th>Medication</th>
<th>Summary of Prescribing Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMITRIPTYLINE</td>
<td>ANTICHOLINERGIC/ SEDATING</td>
</tr>
<tr>
<td>BARBITURATES</td>
<td>SEDATING / HIGHLY ADDICITIVE</td>
</tr>
<tr>
<td>LONG-ACTING BENZODIAZEPINES EX DIAZEPAM</td>
<td>LONG ACTING SEDATION/ FALLS</td>
</tr>
<tr>
<td>CHLORPROPRAMIDE</td>
<td>HYPOGLYCEMIA, SIADH</td>
</tr>
<tr>
<td>BELLADONNA ALKALOIDS-EX DICYCLOMINE</td>
<td>ANTICHOLINERGIC / HIGHLY TOXIC</td>
</tr>
<tr>
<td>DIGOXIN &gt;0.125MG</td>
<td>SMALL THERAPY WINDOW/ POOR CL</td>
</tr>
</tbody>
</table>
## Beers List: High Potential for Severe Adverse Outcome

<table>
<thead>
<tr>
<th>Medication</th>
<th>Summary of Prescribing Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disopyramide</td>
<td>May induce heart failure</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Anticholinergic / Sedating</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Erratic oral / Clearance</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>Highly addictive / Sedating</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Bradycardia / Depression</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>Confusion / Hallucinations</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Aspirin w/ Neutropenia</td>
</tr>
</tbody>
</table>
I TOLD YOU
I WAS SICK
BASTARDS
<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>SUMMARY OF CONCERN</th>
<th>MEDICATION</th>
<th>SUMMARY OF CONCERN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benadryl</td>
<td>Anticholinergic</td>
<td>Dipyridamole</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Ergot Alkyloids</td>
<td>Ineffective</td>
<td>Antihistamine</td>
<td>Anticholinergic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“sedating “</td>
<td></td>
</tr>
<tr>
<td>Indocin</td>
<td>CNS S/E</td>
<td>Phenyl-Butazone</td>
<td>Blood Dyscracias</td>
</tr>
<tr>
<td>Muscle Relaxants</td>
<td>Sedating Confusion</td>
<td>Reserpine</td>
<td>Depression</td>
</tr>
</tbody>
</table>
Potentially Inappropriate Medications: Zhan Criteria

- Based on the 1997 version of the Beer’s criteria, the Zhan criteria focus only on drugs that should generally be avoided in elders, without consideration of drug dosages, drug-disease interactions, or drug-drug combinations. The Zhan criteria categorize drugs into one of three categories: drugs that should always be avoided (e.g., meperidine), drugs that are rarely appropriate (e.g., diazepam), and drugs that are sometimes appropriate but often misused (e.g., amitriptyline).

- Zhan: JAMA 2001;286:2823-2829
Extent of Potentially Inappropriate Prescribing in the Elderly (PIPE)

- **Design**: Retrospective analysis of VA database (FY00) using Beers and AHRQ (Zhan) criteria to determine PIPE.

- **Participants**: Veterans >65, w/ outpatient visits VA facility (N=1,265,434)

- **Measurements**: Inappropriate use based on Beers-(drug, dose, drug disease) and Zhans (drug to be avoided), duration, patient characteristics associated with PIPE were analyzed/described.
PIPE

• Results: Applying mentioned criteria PIPE decreased from 33% to 23%.

• Most common inappropriate medications were pain relievers, benzos, antidepressants and musculoskeletal agents-61% of PIPE.

• Those with Psych comorbidities, most likely to receive inappropriate drugs. Women more likely to receive Zhan drug.

• QUESTION: is the use of medications from a list / criteria always PIPE?

Can a List or Criteria Stop Inappropriate Prescribing?

- VA Iowa City 256 pt’s >65 on >5 medications. (3678 meds total). Comprehensive medication interview by MD/Pharmacist team.

- Same patients and their medications were evaluated strictly using Beer’s / Zhan Criteria.

- Beer’s Criteria flagged 214 (6%) & Zhan criteria flagged 91 (2.5%) as potentially inappropriate.
Can a List or Criteria Stop Inappropriate Prescribing?

• Pharmacist/MD team identified 563 medications (15%) as PROBLEMATIC!

• Approximately 50% of the medications deemed potentially inappropriate by Beer’s or Zhan Criteria were not judged to be problematic by the TEAM.

• CONCLUSION: can be used as initial guides BUT are not accurate to use as stand alone criteria to judge quality prescribing!

• Steinman: Arch. Intern Med. 2009 July 27th, 1326-1332
STOP PIPE

- Avoid prescribing prior to diagnosis.
- Always consider PK, PD, DI’s and geriatric prescribing criteria.
- Start with low dose and titrate slowly
- Avoid starting 2 agents at the same time.
- Avoid prescribing to treat side SE of other drug.
- Avoid therapeutic duplication.
- Always have a plan, monitoring and endpoint before prescribing.
Case Study 1

- JB is a 77 y/o female residing in a nursing home. HX CHF, complaints of GI distress, anxiety, sleep disturbance.
- Wt- 112 lbs. Scr=1.0
- Medications: Ranitidine 150mg BID, Digoxin 0.25mg QD, Diazepam 5mg QHS.
- Which medications may be deemed inappropriate and why?
Case Study 1-Discussion

- **CrCl**
  \[(\text{IBW in Kg}) \times 140 - \text{age} \times 0.85 \text{ for females}\]
  \[72 \times \text{SCr}\]
  \[\approx 37 \text{ ml/min}\]
- Ranitidine <50 ml/min decrease to once daily (s/e CNS h/a, dizzy, confusion).
- Digoxin >0.125mg, use CHF? (s/e CNS GI)
- Diazepam note recommended
- If needed consider (LOT).
Case Study 2

• CK is an 82 y/o male residing at home. HX of BPH, insomnia, COPD and chronic pain

• Medications include: Indocin 50mg BID, Tylenol PM, Combivent Inhaler 2 puffs QID.

• Which medications may be deemed inappropriate and why?
Case Study 2 Discussion

- Tylenol PM contains Benadryl not appropriate in the elderly or pt’s with BPH (anticholinergic effect CNS/ bladder).
- Indocin only appropriate in GOUT not general pain due to CNS S/E.
- May consider long acting inhaler for COPD tiotropium with albuterol PRN – better compliance.
QUESTIONS?

AMERICAN HEALTHCARE
As good as ever