PHARMACODYNAMICS OF AGING:
NARROWING OF THE THERAPEUTIC INDEX IN
THE FACE OF THERAPEUTIC OPPORTUNITY

Darrell R. Abernethy, M.D., Ph.D.
Associate Director for Drug Safety
Office of Clinical Pharmacology
Food and Drug Administration

Table 1. Age-related chronic medical conditions*

<table>
<thead>
<tr>
<th>MEDICAL CONDITION</th>
<th>FREQUENCY PER 1000 PERSONS IN USA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt;45 y</td>
</tr>
<tr>
<td>Arthritis</td>
<td>30</td>
</tr>
<tr>
<td>Hypertension</td>
<td>129</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>37</td>
</tr>
<tr>
<td>Heart disease</td>
<td>33</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>19</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
</tr>
</tbody>
</table>

Cardiovascular Pharmacodynamics of Aging

Pharmacokinetics of Aging

Multimorbidity and Polypharmacy

Assessment of Functional Effects of Polypharmacy

Alterations in the Cardiovascular System of the Elderly

Cardiovascular hemodynamics
- Tendency to contracted intravascular volume
- Increased peripheral vascular resistance
- Tendency to lowered cardiac output
- Decreased baroreceptor sensitivity
- Increased blood pressure variability
- Suppressed plasma renin activity
- Decreased vascular endothelium production of nitric oxide
Arterial Changes Related to Aging

- Increased Calcium and Collagen
- Reduces Elasticity and Compliance
- Increased Pulse Pressure
- Decreased Baroreceptor Sensitivity
- Hyaline Thickening in Arterioles, Small Arteries
- Increased Peripheral Resistance
HEART RATE RESPONSES

- DECREASED RATE RESPONSES
  Parasympathetic
  Sympathetic

- DIFFERING SENSITIVITY TO CALCIUM CHANNEL BLOCKADE OF THE SINUS NODE
Pharmacokinetics of Aging

Figure 2. Scatterplot of correlation of age and peak (percent of control values) coronary blood flow response to acetylcholine.

Chauhan, et al. JACC, 1996; 28: 1796-1804
Drug Phase I enzymes

Oxidation Reduction Hydrolysis

Phase II Conjugated enzymes metabolites

Metabolites

Some Phase I Drugs

CYP1A2
- duloxetine
- olanzapine

CYP2C9
- phenytoin
- warfarin

CYP2C19
- diazepam
- phenytoin
- clopidogrel

CYP2D6
- carvedilol
- duloxetine

CYP3A
- midazolam
- cyclosporine
- clarithromycin
- amlodipine

PARTIAL LIST OF DRUGS THAT UNDERGO SIGNIFICANT RENAL EXCRETION IN HUMANS

- Amantadine
- Aminoglycoside antibiotics
- Cimetidine
- Digoxin
- Furosemide
- Lithium
- Nitrofurantoin
- Ouabain
- Penicillin antibiotics
- Phenobarbital
- Quinidine
- Sulfonamides
- Tetracycline

COCKCROFT & GAULT EQUATION

\[
CL_{Cr} = \frac{(140 - \text{age}) \times \text{weight in kg}}{72 \times \text{serum Cr in mg/dL}}
\]

[reduce estimate by 15% for women]
<table>
<thead>
<tr>
<th>PHARMACOKINETIC CHANGES IN THE ELDERLY</th>
<th>CHANGE WITH AGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Absorption</td>
<td>none</td>
</tr>
<tr>
<td>Drug Distribution</td>
<td></td>
</tr>
<tr>
<td>Central Compartment Volume</td>
<td>none or ▼</td>
</tr>
<tr>
<td>Peripheral Compartment Volume</td>
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</tr>
<tr>
<td>Lipophilic Drugs</td>
<td>▼▼</td>
</tr>
<tr>
<td>Hydrophilic Drugs</td>
<td></td>
</tr>
<tr>
<td>Plasma Protein Binding</td>
<td>▼</td>
</tr>
<tr>
<td>Binding to Albumin</td>
<td></td>
</tr>
<tr>
<td>Binding to α1-acid Glycoprotein</td>
<td>none or ▲</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>PHARMACOKINETIC CHANGES IN THE ELDERLY</th>
<th>Change with Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Elimination</td>
<td></td>
</tr>
<tr>
<td>Renal Elimination</td>
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<tr>
<td>Hepatic Elimination</td>
<td></td>
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<tr>
<td>Phase I Reactions</td>
<td></td>
</tr>
<tr>
<td>CYP3A</td>
<td>▼</td>
</tr>
<tr>
<td>CYP1A2,2D6,2C9,2C19,2E1</td>
<td>☞ or ▼</td>
</tr>
<tr>
<td>Phase II Reactions</td>
<td></td>
</tr>
<tr>
<td>Glucuronidation</td>
<td>☞</td>
</tr>
<tr>
<td>Sulfation</td>
<td>☞</td>
</tr>
<tr>
<td>Acetylation</td>
<td>☞</td>
</tr>
</tbody>
</table>

Multimorbidity and Polypharmacy
Assessment of Functional Effects of Polypharmacy: Anticholinergic and Sedative Drugs

Older people carry

High burden of illness: medications indicated

Increased risk adverse drug events

Limited evidence base to guide prescribing

Need evidence based model to assess functional risk/benefit
Equation Derived for Drug Burden Index (DBI)

\[ DBI = \sum \frac{D_{AC}}{\delta_{AC} + D_{AC}} + \sum \frac{D_S}{\delta_S + D_S} \]

DBI: Drug Burden Index  
AC: Medications with anticholinergic properties  
S: Medications with sedative properties  
D: Daily dose  
\( \delta \): Minimum recommended daily dose approved by US Food and Drug Administration; estimate of DR_{50}

Functional Measures

- Physical function — Health ABC Score (HABC)
  - Objective measures:
    - Chair stands
    - 6 m walk
    - Narrow 6 m walk
    - Standing balance
  - Higher score, better physical function
  - Validated (Established Populations for Epidemiologic Studies of the Elderly)

- Digit Symbol Substitution Test (DSST)
  - Psychomotor performance, attention, concentration, STM
  - Higher score, better cognitive function
  - Validated (Wechsler Adult Intelligence Scale)

Association of Anticholinergic Burden with Function and Sedation
Association of Sedative Burden with Function and Sedation

Relative Impact of Drug Burden Index on Function

- Multiple regression analysis
- Degree of variance in HABC score captured by a one point increase in drug burden index is:
  - ~ 3 additional physical co-morbidities
  - > cog impairment, depression or anxiety

Longitudinal Association Between DBI and Function in Health ABC Study Participants

Association of
- Drug Burden Index at each time point
- Cumulative drug burden exposure
  with function over 5 years
Conclusions

• In Health ABC participants, Drug Burden Index at years 1, 3 and 5 and total drug burden exposure (AUCDB) are associated with reduced functional performance at year 6.

Other Populations

• Womens Health and Aging Study (WHAS) – Community dwelling frail older women (USA)
• Concord Health in Ageing Men Project (CHAMP) – Community dwelling older men (Australia)
• FREEDOM – Older people living in low level residential aged care (Australia)
• Department of Veterans Affairs – DVA linked data bases (Australia) - pending

Why Include Patients with Multiple Chronic Conditions (mostly older) in Clinical Trials?

• Efficacy
  – Is the same therapeutic benefit seen on the background of multiple illnesses and medications used to treat them?
  – Should the trial be powered to independently assess efficacy for the MCC patients?
• Safety
  – Is the safety profile adequately characterized without direct study of the MCC patient population?
  – What are the "off-target" drug effects that may have particular impact in MCC patients?

Are Older Patients Being Included?
Older Patients with MCC?
Goals for Treating the Older Patient

- ↓ Morbidity & Mortality
- Avoid or Minimize Drug-Related Problems
- Improve the Quality of Life

By the time a man gets well into the seventies, his continued existence is a mere miracle

R.L. Stevenson: AES Triplex

“Come grow old along with me, the best of things are yet to be.”

“Rabbi Ben Ezra,”
Robert Browning (1812 – 1889)